Volume XXI Number 6

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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

JUNE
1960

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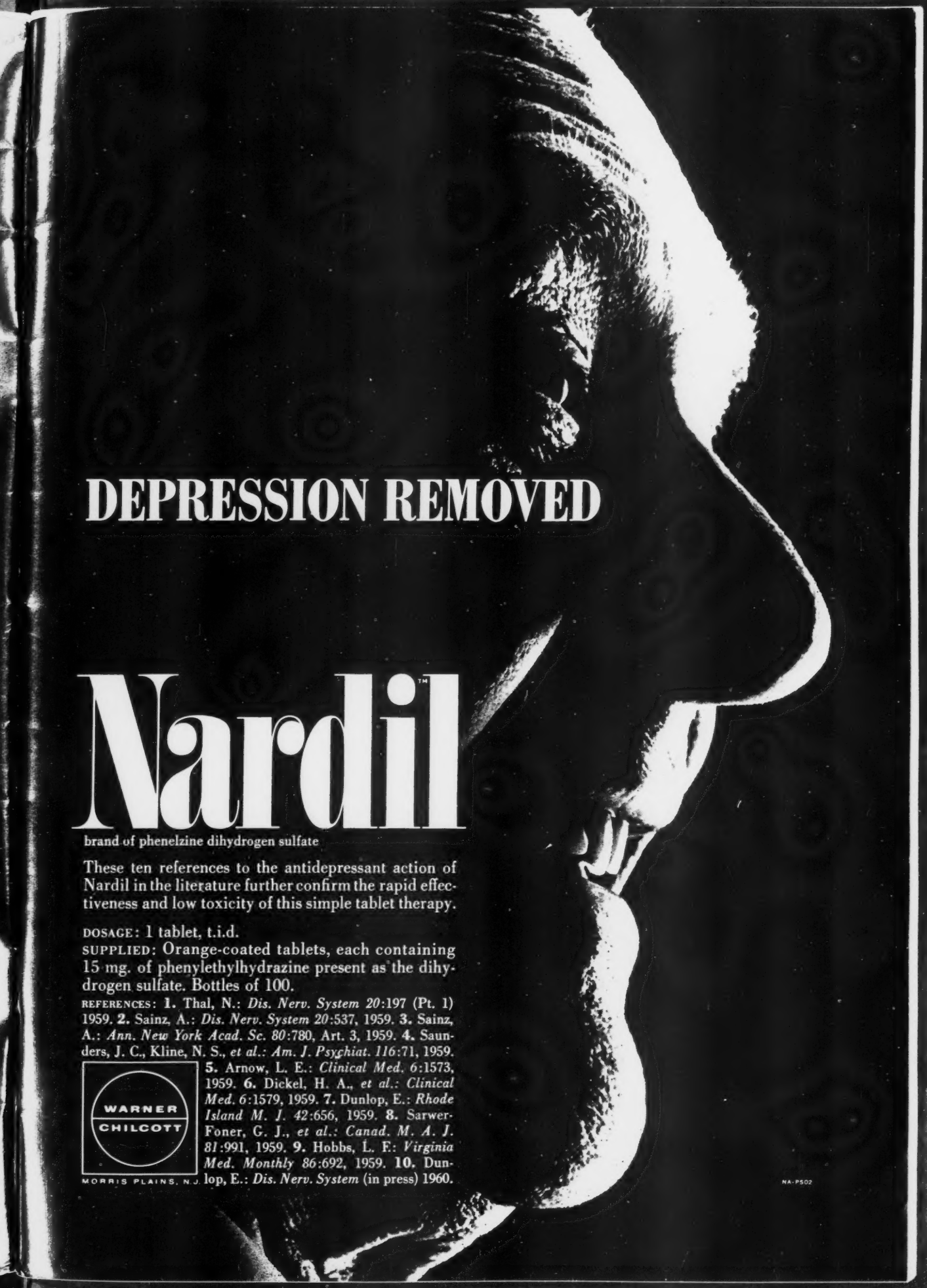

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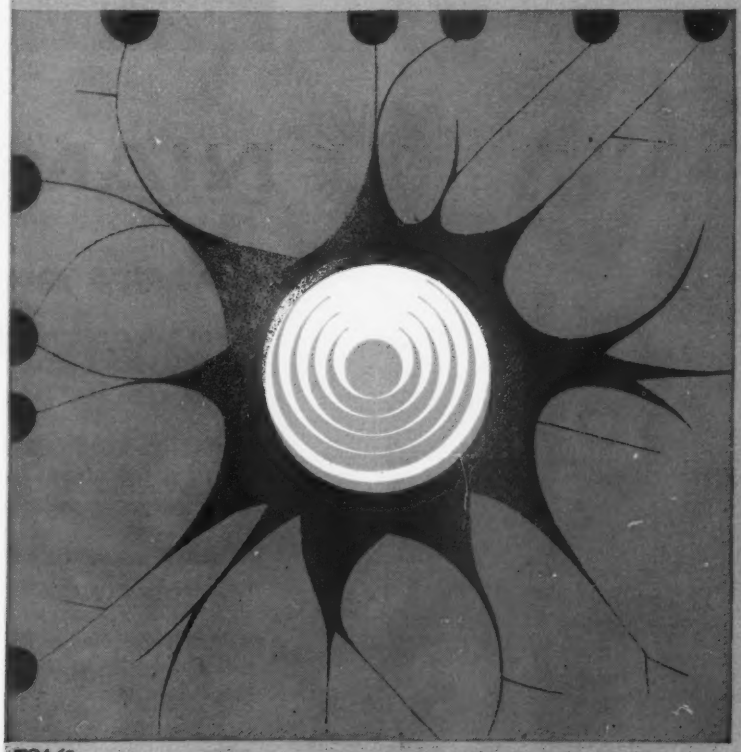

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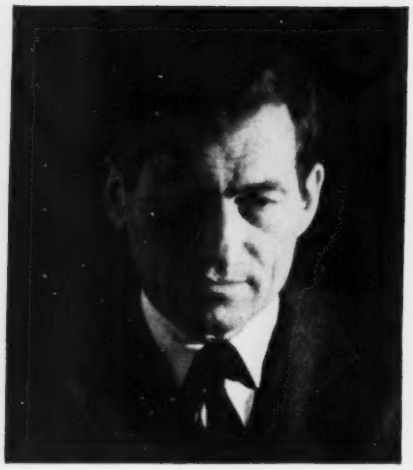

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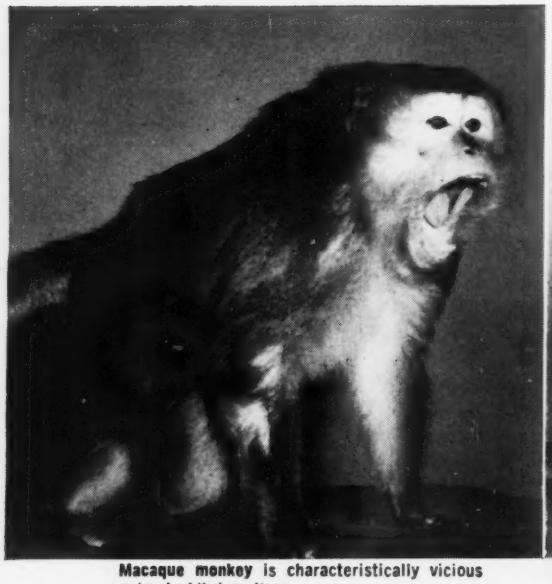
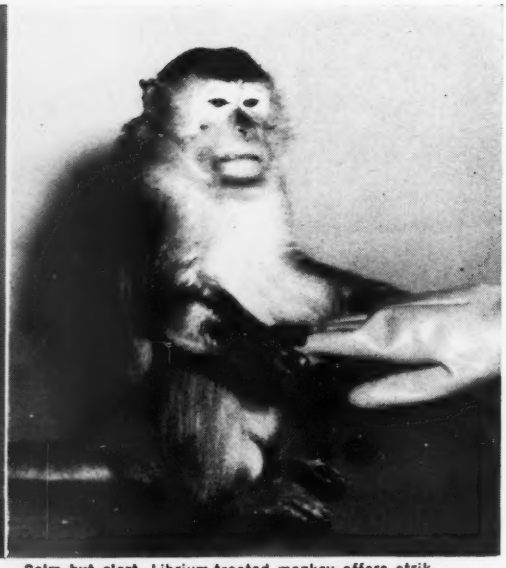


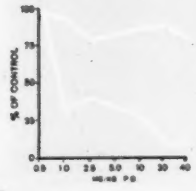
Macaque monkey is characteristically vicious prior to Librium therapy.



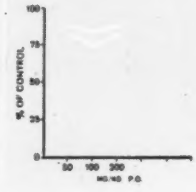
Calm but alert, Librium-treated monkey offers striking contrast to "doped-up" appearance observed with reserpine and phenothiazine derivatives.

taming effect of Librium on rats, monkeys and mice

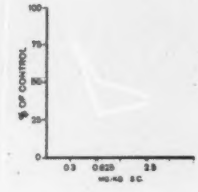
EFFECT ON ACTIVITY AND AGGRESSION IN MONKEYS[2] Legend: activity aggression



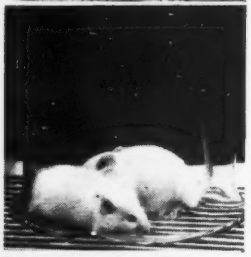
Librium[T.M.] Aggression dramatically reduced; **level of activity normal**



Meprobamate No decrease in aggression; slight reduction of activity



Chlorpromazine Aggression reduced; **precipitous decrease in activity**



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1. Allen, V. S.: Trifluoperazine in the Treatment of Drug-Resistant Schizophrenics, J. Clin. & Exper. Psychopath. *20*:247 (Sept.) 1959.

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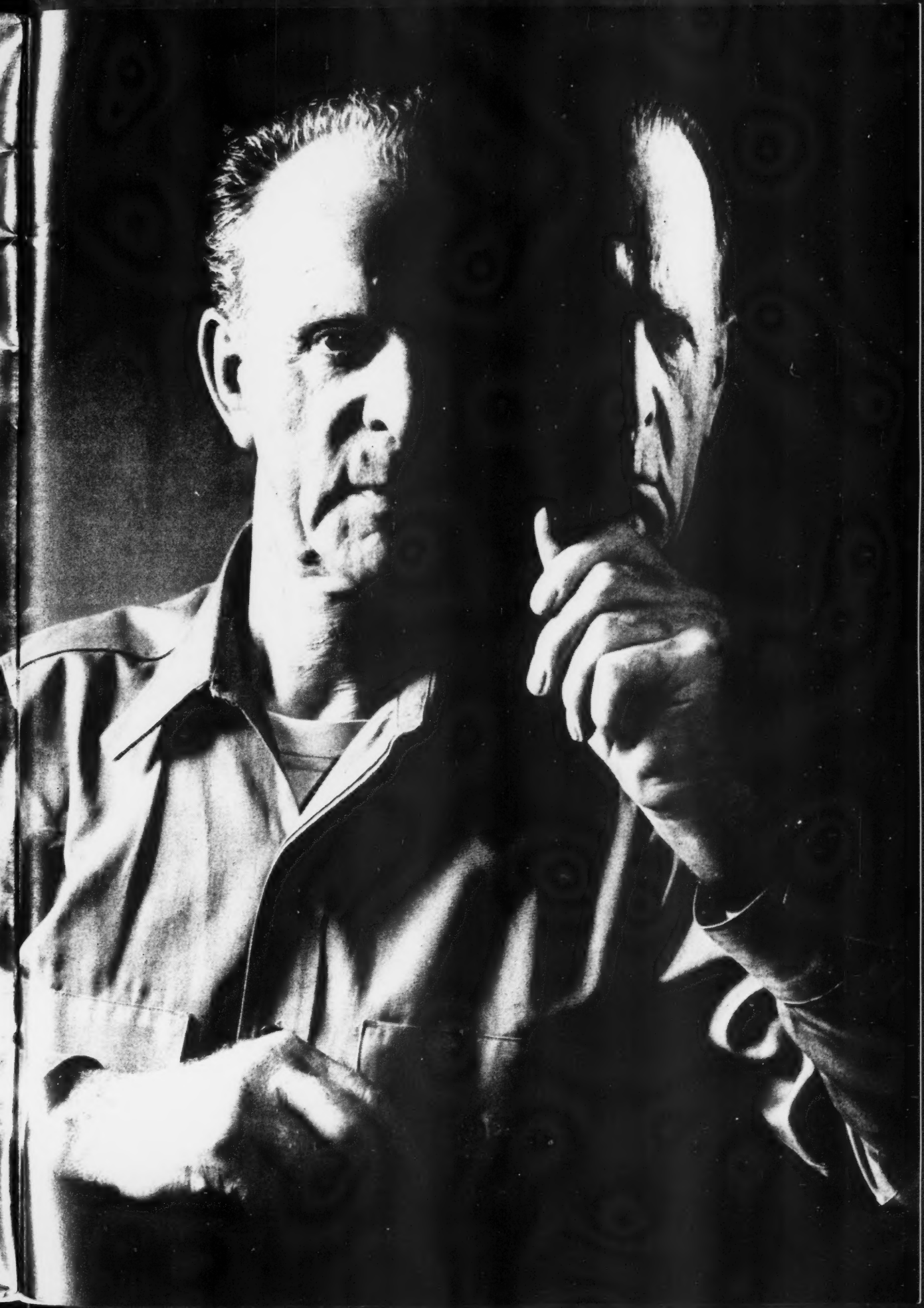

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Bibliography *(11 clinical studies, 764 patients):*

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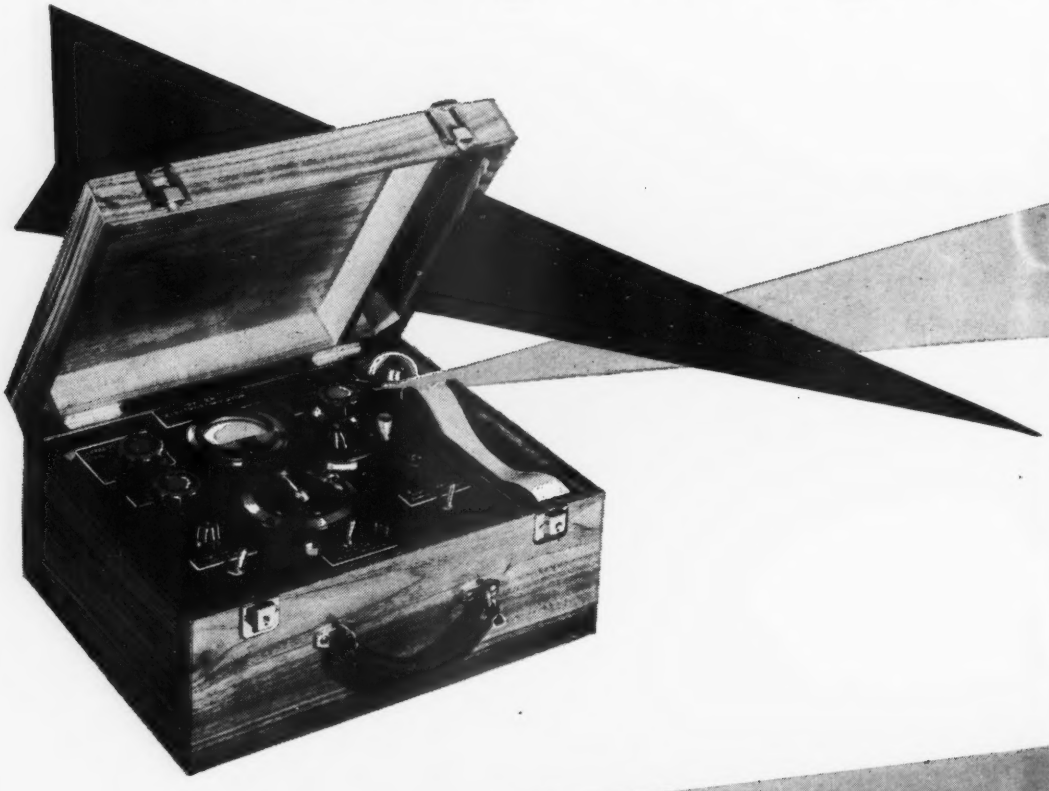

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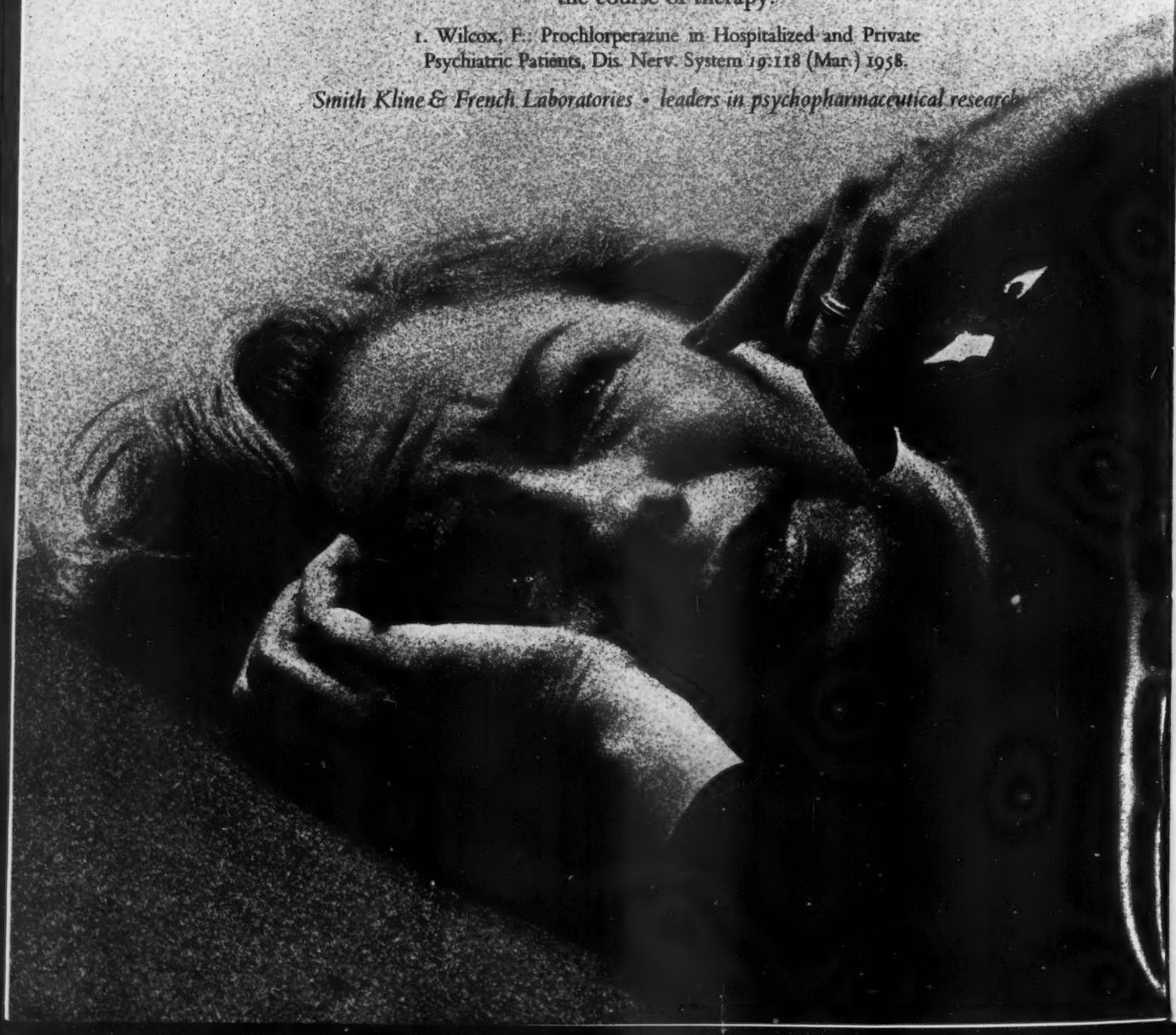

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DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Causes of Death in Hospitalized Veterans with Neuropsychiatric Disorders

LEO E. HOLLISTER, M.D., JOHN J. PRUSMACK, M.D., and ROY S. HUBBS, M.D.

Patients hospitalized for neuropsychiatric disorders have a mortality rate greater than that of the general population. Average life expectancy of hospitalized schizophrenics in a Swedish study was found to be only three-quarters normal.[1] Crude death rate of patients in Michigan State Hospitals, even though declining somewhat faster than that of the general population, was 3.6 times higher after adjustments for age and sex.[2] During the first year of hospitalization, schizophrenics had a death rate twice that of normal in New York,[1] while mental hospital patients as a whole had a death rate 10 times normal in Scandinavia.[3] The greatest disparity in death rates was found in the 20 to 24-year age-group in which mortality was 13.2 times that of a comparable group of the general population.[2]

The present study reviews the principal and contributing causes of death in patients of one mental hospital and delineates some of the special medical problems such patients present.

Description of Sample

All deaths among neuropsychiatric patients during a 12½ year period (1947-1959) in a 1340-bed neuropsychiatric hospital were considered; 498 deaths were recorded with post-mortem examinations obtained on 348, approximately 70%. Even when post-mortem examination was not obtained, clinical study prior to death established a reasonably accurate cause of death.

From Veterans Administration Hospital, Palo Alto, California.

Distribution of deaths by three broad psychiatric diagnostic categories (functional psychoses, chronic brain syndromes, and neurologic diseases associated with disorder) is shown in Table I. Schizophrenic reactions and chronic brain syndromes due to arteriosclerosis and syphilis were the psychiatric diagnoses in more than two-thirds of all deaths. Age-distribution at time of death is shown in Table II. Over 80% of all deaths occurred in patients more than 50 years of age. Median age at time of death was lowest in patients with neurologic diseases, highest in patients with chronic brain syndromes. Range of ages at death was from 22 to 95 years. All but three of the patients in this series were men.

Certain biasing factors were present in this sample. First, it was composed exclusively of military veterans whose hospital admission was predicated in most instances upon their psychiatric disorder being con-

TABLE I

Distribution of Deaths by Diagnostic Category

	Autopsy	Non-Autopsy	Total
Functional Psychoses	148	81	229
Scizophrenic reactions	127	70	197
Affective disorders	20	11	31
Other	1	0	1
Chronic Brain Syndromes	152	59	211
Senile and pre-senile	23	10	33
Arteriosclerosis	54	33	87
Syphilis	64	11	75
Alcohol	11	5	16
Neurologic Diseases	48	10	58
Totals	348	150	498

nected with military service. Second, the predominance of men tended to favor prevalence of certain diseases over others. Third, local hospital policies influenced the handling of certain types of patients. For instance, over the first half of the sampling period, the hospital had a tuberculosis service with some deaths from pulmonary tuberculosis. Later, this service was closed and patients with tuberculosis were transferred to other hospitals. Despite such biasing factors, the sample provided information regarding causes of death in Veteran neuropsychiatric patients who occupy 70,000 hospital beds in the United States.

Principal Causes of Death

Distribution of the primary causes of death modified from the International Classification of Causes of Death is shown in Table III. Diseases of the circulatory and respiratory systems accounted for the majority of deaths, each category being far larger than any other.

Infectious diseases accounted for 33 deaths, 26 being from pulmonary tuberculosis. The remainder died of infections of the gastrointestinal tract, mainly acute enterocolitis or colitis. In the latter cases, a specific organism could not always be isolated. Three cases of fatal enterocolitis followed the importation of food to the hospital by relatives, leading to a strict interdiction of this practice.

Neoplasms of the lung or colon accounted for 24 of the 44 deaths from malignancies. Other organs involved were the stomach, pancreas, liver and biliary system, kidney, prostate, brain, larynx, and bone marrow (plasma-cell myeloma) in that order.

Allergic, endocrine, metabolic and nutritional disorders were responsible for only six deaths, three being due to malnutrition. Amyloidosis secondary to pulmonary tuberculosis, disseminated lupus erythematosus

TABLE II

Age Range at Death: All Cases

Age	Functional Psychoses	Chronic Brain Syndromes	Neurologic Diseases	Total
20-29	9	1	3	13
30-39	30	2	10	42
40-49	20	4	9	33
50-59	64	53	16	133
60-69	94	75	14	183
70 or over	12	76	6	94
				498
Median Age	59 years	65 years	56 years	

TABLE III

Primary Causes of Death: International Classification

	FP		CBS		ND		
	Autopsy	Non-Autopsy	Autopsy	Non-Autopsy	Autopsy	Non-Autopsy	Total
Allergic, endocrine,							
Infectious Diseases	14	7	9		3		33
Neoplasms	25	6	5	4	4		44
metabolic, nutritional disorders	1		1	2		2	6
Blood diseases	3						3
Nervous system	5	3	2	8	1		19
Circulatory system	62	16	59	24	7	1	169
Respiratory system	11	12	52	16	23	4	118
Digestive system	8	1	14	3	3		29
Genitourinary system	3	4	4	1	1		13
Accidents, suicides	16	19	6		6	1	48
Cause unknown		13		1		2	16
	148	81	152	59	48	10	498

Total, 498 cases, 348 autopsied.

FP—Functional Psychoses; CBS—Chronic Brain Syndrome; ND—Neurologic Diseases.

TABLE IV

Significant Associated Conditions: 348 Autopsied Cases

	Functional Psychoses	Chronic Brain Syndrome	Neurologic Diseases	Total
Infectious diseases	10	17	3	30
Neoplasms	6	8	3	17
Allergic, endocrine, metabolic, nutritional disorders	10	10	2	22
Nervous system	7	2	1	10
Circulatory system	49	112	15	176
Respiratory system	23	45	15	83
Digestive system	63	76	14	153
Genitourinary system	47	90	18	155

secondary to a penicillin reaction, and disseminated platelet thrombosis due to unknown cause accounted for the remaining deaths.

Blood diseases caused three deaths, but these were considered to be secondary to toxic or drug reactions. One case of acute purpura was considered secondary to reserpine administration; one case of pancytopenia secondary to chloramphenicol terminated with a subarachnoid hemorrhage; a third patient died of aplastic anemia, the etiologic agent not being specified.

Nervous system diseases: Only 19 patients died of acute strokes. The type of cerebral vascular disorder was listed as intracerebral hemorrhage in eight cases, cerebral thrombosis in seven, embolization in two, and subarachnoid hemorrhage in two. Arteriosclerosis and hypertension were the most commonly associated conditions.

Circulatory system diseases: Of 169 deaths in this category, 76 were due to infarction of the myocardium and 69 due to congestive heart failure. Arteriosclerosis was the major etiologic factor in both categories. Hypertension played a contributing role in eight cases of myocardial infarction, hemorrhage into arteriosclerotic plaques in four, and other factors in six. The remaining cases of myocardial infarction were primarily due to arteriosclerosis. The median age of death from congestive heart failure was 61 years, with a range of 26 to 90 years. The median age from myocardial infarction was 63 years, with a range of 24 to 86 years. Of 13 deaths from pulmonary infarction, underlying causes were congestive heart failure in two, myocardial infarction in two, and one case each with thrombophlebitis, carcinoma of the prostate, post-operative shock, pulmonary emphysema, and steroid therapy.

Respiratory system diseases were particularly frequent in patients with chronic brain syndromes and neurologic diseases. Bacterial pneumonias, either bronchopneumonic or lobar, accounted for 77 of 118 respiratory deaths. As might be expected, most cases occurred in elderly and debilitated patients, complicating or terminating chronic illness. A similar situation obtained in 30 deaths from aspiration pneumonia. Chronic lipoid pneumonia from aspiration of mineral oil caused four deaths prior to discontinuation of its use as a laxative in 1951. Four patients died of pneumonia complicating influenza, two had staphylococcal pneumonia, and one patient with severe bulbous emphysema died of bilateral pneumothorax.

Digestive system diseases: Of 29 deaths from these disorders, complications of peptic ulcer were most frequent, accounting for 13. The prevalence of peptic ulcer is generally high in mental hospital populations, though difficult to detect because of dearth of symptomatic complaints. Hemorrhage or perforation was the usual complication, being the only clinical manifestation in several patients. Fatal acute abdominal conditions were largely due to difficulty or delay in detecting these complications in psychotic patients. Four patients died of volvulus, three of cholecystitis, two of strangulated hernia, and one of acute appendicitis.

Genitourinary system diseases contributed to 13 deaths; pyelonephritis accounted for five, one being associated with amyloidosis of the kidney. Other causes of renal failure were nephrosclerosis in four cases, glomerulonephritis in three, and thrombosis of the renal veins in one.

Accidents, suicides were responsible for 48 deaths, of which 30 were accidental. Median ages of these patients were somewhat lower than for the whole group, being 49 years for accidental deaths, and 41 years for suicides. Most accidental deaths occurred in the hospital. In 10 instances, death resulted from treatment such as complications of insulin-coma therapy, transfusion reaction, post-operative hemorrhage, and perforation of the colon from an enema tube. Ten deaths from asphyxia were due to aspiration of food, vomitus, or other foreign bodies, or associated with convulsive disorders. Most suicides occurred outside the hospital while patients were on leave or elopement status. Although the majority of suicides are listed as not having been autopsied at this hospital, coroners' offices performed post-mortems in

these cases. All 18 suicides were patients with functional psychoses, only four of whom had a diagnosis of affective disorder.

Cause unknown was recorded in 16 patients who died while on authorized leave from the hospital. These patients tended to be slightly younger than the entire group. A few of them were known to have coronary arteriosclerosis, which could have led to sudden death.

Significant Associated Conditions

The prevalence of significant associated conditions in the 348 autopsy cases is shown in Table IV. Cardiovascular disease and respiratory disease were again prominent. However, the prevalence of renal and gastrointestinal diseases as contributing causes of death was strikingly higher than as major causes of death.

Infectious diseases, notably pulmonary tuberculosis, probably slightly active, was present in 21 cases. Four additional cases of pulmonary granulomata suggesting residuals of tuberculosis were encountered, but this etiology could not be established. Five patients had enteritis or colitis, usually as a terminal condition.

Neoplasms: Latent carcinoma of the prostate was found in 10 patients dying from other causes. Seven others had various types of malignancies which did not constitute the major cause of death. These included carcinoma of the bladder, larynx, liver, lung, and Hodgkin's disease.

Allergic, endocrine, metabolic, nutritional disorders: Pathologic evidence of diabetes was present in 10 patients, manifested as hyalinization of beta cells of the pancreas. Intercapillary glomerulosclerosis was also noted in four patients. Amyloidosis, secondary to chronic pulmonary tuberculosis or renal infection, was present in four patients.

Nervous system diseases: Residuals of major cerebral vascular accidents were found as significant associated conditions in seven cases. Chronic subdural hematoma was found in three patients, none of clinically significant degree.

Circulatory system diseases: Cardiovascular disease was a significant associated condition in 176 patients; 61 had arteriosclerotic complications, either frank myocardial infarction or advanced coronary arteriosclerosis. Pulmonary infarction was found in 10. Evidence of rheumatic endocarditis was present in only 12. Of 35 patients classified as having chronic brain syndrome associated with syphilis, 30 had evidence of syphilis of the aorta, contrary to the frequently quoted clinical dictum that when the nervous system is attacked, the vascular system is spared. On the other hand, calcific aortic stenosis was an uncommon finding, even at post-mortem, and in most instances, was diagnosed accurately prior to death. So-called non-bacterial thrombotic endocarditis was found in 12 patients, being associated with congestive heart failure or myocardial infarction in five, malignancies in three. In one instance, this condition was apparently the sole source of widespread cerebral and systemic embolization; in another, it was part of a generalized angiitis, probably representing Libman-Sack's disease. The aortic and mitral valves were affected in about equal proportion.

Respiratory system diseases: Degrees of bacterial or aspiration pneumonia insufficient to cause death were found in 28 of 83 patients with respiratory findings. Pulmonary emphysema was found in 35 instances as a significant associated condition. Lipoid pneumonia was an incidental finding in 17.

Digestive system diseases with abnormalities of the liver, gall bladder, and pancreas accounted for 134 instances of 153 in which gastrointestinal conditions were significant findings. Hepatic abnormalities were most commonly those of fatty infiltration or portal cirrhosis, presumably on the basis of past alcoholism or nutritional problems. Cholecystitis was almost always chronic with stones found in about one-half of the cases. Pancreatic changes were often of the chronic interstitial type, though occasionally acute changes were noted. Uncomplicated peptic ulcers were found in 16 patients.

Genitourinary system diseases: Urinary tract infection was found in 90 of 155 instances of associated diseases. This was

commonly the result of prostatic hypertrophy or neurogenic bladder, each requiring frequent or chronic catheter drainage. Nephrosclerosis (with clinical evidence of hypertension) was found in 48 cases.

Discussion

The mortality rates of these patients was subject to so many biasing factors as to make comparisons difficult. For instance, although the median age at death of patients with functional psychoses and neurologic diseases was lower than expected for a general population of men, both categories of illness included a high proportion of young patients in this sample.

The predominance of circulatory and respiratory system diseases as principal causes of death was similar to other studies of mental hospital patients.[2] Deaths from neoplasms and tuberculosis might have been higher had some of these patients not been transferred to other hospitals for treatment. Neoplasms have been found to be less frequent causes of death in mental patients than in the general population, while tuberculosis is more frequent.[2] The latter disease no longer occupies a prominent place as a cause of death in mental patients, due both to improved case-finding programs and availability of specific treatment.

Myocardial infarction and congestive heart failure were usually diagnosed prior to death when these were the principal causes, although in some instances, the former was evident only by electrocardiographic studies. "Silent" myocardial infarcts would be expected to be high in those mental patients who complain little of pain. On the other hand, as many as 21% of initial myocardial infarcts in normal middle-aged persons may also be "silent."[4] Arteriosclerosis, underlying most instances of congestive heart failure and myocardial infarct, was a major disease in these patients.

Pneumonia was especially frequent as a cause of death in patients with chronic brain syndromes and neurologic diseases, recurrent attacks often preceding the final episode. In such instances, even prompt and vigorous antibacterial treatment was usually of no avail. Classical lobar pneumonia was less frequent than patchy or confluent bronchopneumonia. Aspiration and lipoid pneumonia were complications in debilitated patients with swallowing difficulty.

Acute abdominal emergencies (complicated peptic ulcers, volvulus of small or large bowel, cholecystitis) accounted for 21 fatalities. Recognition of these disorders may be delayed by failure of patients to correctly interpret pain or report it. As many as 21% of psychotic patients with perforated ulcers and 37% with acute appendicitis failed to experience pain in one series.[5] Although only one patient died from acute appendicitis, the majority of operated cases of appendicitis in our psychotic patients have perforated prior to operative intervention.

Vigorous and active treatment programs in any field of medicine entail risks. Therapeutic accidents in this series were infrequent causes of death. With the abandonment of leucotomy and the sharp decline in electroconvulsive and insulin shock therapy, therapeutic accidents have declined somewhat. However, the drug therapies which have replaced these treatments carry a risk of their own. Suicides of mental patients appear to be increasing in recent years. To some extent, this rise parallels the trend toward "open" hospitals and earlier release. Here, too, a therapeutic gain for the majority may constitute a risk for a minority of patients.

Among significant associated conditions, circulatory system diseases still predominated. Both genitourinary and digestive system diseases were more important as contributory causes than as primary causes of death. Urinary infection in hospitalized geriatric patients is frequent at post-mortem and almost the rule in cases where catheter drainage has been employed chronically. The high prevalence of hepatobiliary disease in this group was striking. Nutritional disturbance may account for many of the hepatic abnormalities encountered. Cholecystitis and cholelithiasis were in concordance with age of the patients and the frequency of arteriosclerotic complications.

While treating these patients, one feels that increased medical facilities in neuropsychiatric hospitals have prolonged some lives but that mortality is still excessive. The major medical problems of arteriosclerotic complications and bacterial or aspiration pneumonia associated with debilitating illnesses are shared with non-psychiatric patients. Special problems among neuropsychiatric patients still contributing to potentially avoidable deaths are "silent" peptic ulcers with complications, "silent" acute abdominal emergencies, treatment accidents (including suicide), and chronic urinary tract infections. Already medical advances have reduced the previously high incidence of tuberculosis in these patients. Future advances in medical care of neuropsychiatric patients may reduce these avoidable deaths still further.

Summary and Conclusions

This study reviews 498 deaths in hospitalized psychiatric patients, of which 70% were examined post-mortem. Median age at time of death was 56 years for patients with neurologic diseases, 59 years in patients with functional psychoses, and 65 years in patients with chronic brain syndromes, suggesting shortened life-expectancy in the first two groups. Circulatory and respiratory system diseases accounted for 287 deaths. Lobar or bronchopneumonia, myocardial infarction and congestive heart failure were the most frequent principal causes of death, occurring in 222 instances. Significant associated conditions were urinary tract infection in 90, coronary artery disease in 61, liver disease in 57, and gall bladder disease in 52.

Most deaths (21) from remediable conditions were from acute abdominal emergencies. The difficulties in diagnosis of these conditions in patients with impaired responses to pain is great. Fatal therapeutic accidents or complications occurred in 12 patients, and suicides in 18. These may represent the cost of an active and vigorous treatment program aimed at helping the majority of patients.

The major medical problems of these patients (arteriosclerotic complications and pneumonias associated with chronic disease) are shared with non-psychiatric patients. Special problems still to be solved are delay in recognition and treatment of acute abdominal emergencies or complications of peptic ulcer, minimizing treatment accidents, and controlling chronic urinary tract infections.

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EASTERN PSYCHIATRIC RESEARCH ASSOCIATION WORLD TOUR-1960

A group representing the Eastern Psychiatric Research Association will depart from New York City on July 1st on a good will and scientific exchange world tour lasting six weeks. The tour will include stop-overs in California, Hawaii, Japan, Hong Kong, Thailand, India, Iran, Israel, and France. Psychiatric meetings will be held in conjunction with the psychiatric societies of Tokyo, Hong Kong, Bangkok, India and Israel. For information, contact David J. Impastato, M.D., 40 Fifth Ave., New York, N. Y.

Electrical Stimulation of the Human Brain Through Implanted Electrodes: Preliminary Observations

GIAN EMILIO CHATRIAN, M.D., MAGNUS C. PETERSEN, M.D.,
and ALFRED UIHLEIN, M.D.

As a part of a series of depth electrographic investigations of human subjects, observations of the effects of electrical stimulation of various deep cerebral regions through implanted electrodes have been made at the Rochester State Hospital since 1952.

Following indication that monophasic pulses produce injury to nerve cells (Lilly and associates[1]) analogous to the injury produced by small direct currents (Ranson and Ingram[2]), the use of this type of stimulus was discontinued. Now a special electrical stimulation unit has been built that is believed to meet the basic technical and ethical criteria to be considered when dealing with human subjects. As described elsewhere (Chatrian and co-workers[3]), this unit delivers relatively noninjurious short biphasic pulses, controls the stimulus from a distance, makes possible recording during stimulation of the induced cerebral responses, produces only minimal artefacts, and provides for recording of the stimulating pulses with adequate measurement of voltage, current, and interelectrode impedance. This report deals with some preliminary results of intracerebral stimulation performed through this unit.

Material and Method

The observations have been in two cases: one patient was suffering from schizophrenic reaction, catatonic type, and the other from chronic brain syndrome associated with convulsive disorder that was supposed to be secondary to a parasagittal focus. Frontal lobotomy was selected for treatment of the former patient and cortical excision for the latter. In both subjects depth multielectrode leads (Chatrian and co-workers[4,5]) were implanted in the brain through the burr holes to be used for operation.

Before the surgical treatment was carried out, a total of 698 stimulations through 56 intracerebral electrodes were given these patients over a period of five weeks for one and four weeks for the other. The observations were made during both wakefulness and spontaneous sleep.

The waveform used in these stimulations (Chatrian and co-workers[3]) consists of biphasic pulses obtained by quasi-differentiating the square waves delivered through a stimulator (Lilly and associates[6,7]). Positive and negative pulses are 60 microseconds each in duration and are separated by a 200-microsecond interval (Hughes[8]). A block diagram of our instrumental arrangement during stimulation is shown in Figure 1. Al-

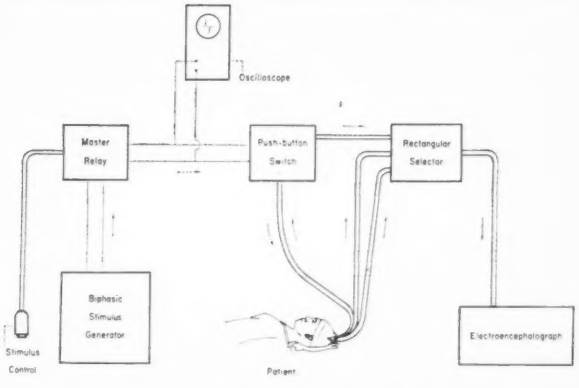

Fig. 1. Simplified block diagram showing instrumental connections during stimulation of intracerebral electrodes. The cable carrying impulses from 21 depth electrodes including the electrode pair to be stimulated is connected to a push-button switch. When the master relay is energized by closing the manual "stimulus control" switch the selected electrodes are connected to the "biphasic stimulus generator." The electrodes not stimulated are connected to the input of a "rectangular selector" switch either through the push-button switch (same cable as electrodes stimulated) or directly (other cables). In turn, the rectangular selector is connected to the input of the EEG apparatus. Dotted arrows indicate direction of travel of stimulating pulses. Plain arrows indicate direction of travel of brain waves.

From Rochester State Hospital and Mayo Clinic, Rochester, Minn.

This study was partially supported by research grants to the Rochester State Hospital from the Minnesota Department of Public Welfare.

though after-discharges can be provoked easily by stimulation with this waveform, we were particularly interested in the electrical responses recorded from various regions of the same and of the opposite hemisphere following stimulation with a single shock or shocks of low rate (1 to 20 pulse-pairs per second). Most commonly, repetitive rates of 1, 3, and 12 pulse-pairs per second during 10 to 60 seconds were used.

Peak currents of 5 to 12.5 ma. (usually 10 ma.) were employed with peak voltages that varied between 9 and 60 v. according to the interelectrode impedance, the average voltage used being 37.5 v. With stainless-steel electrodes the impedance measured averaged 3750 ohms, the lowest value encountered being 1635 ohms and the highest 8000 ohms. These values are lower than those previously found (Chatrian and co-workers[5]) probably because of improvements in the technic of preparation of the electrodes.

The electrical responses are recorded on a 16-channel electroencephalographic assembly. Oscillographic recordings are made by a 4-beam cathode-ray oscillograph used in conjunction with preamplifiers. These tracings are photographed.

Results

Stimulation with single pulse-pairs or with one pulse-pair per second (Fig. 2) via two electrodes located 1 cm. apart along the same intracerebral lead has been found to induce in close or distant regions (or both) of the same and of the opposite hemisphere responses that vary considerably in latency, shape, complexity, size, and duration in the various responsive regions. In conventional EEG tracings these responses appear as spikes, multiple spikes, and sharp waves, alone or associated with slow waves, thus bearing considerable resemblance to some discharges that occur apparently spontaneously in epileptic subjects. The voltage of the responses was at times as much as two millivolts, but their total duration rarely exceeded 500 milliseconds.

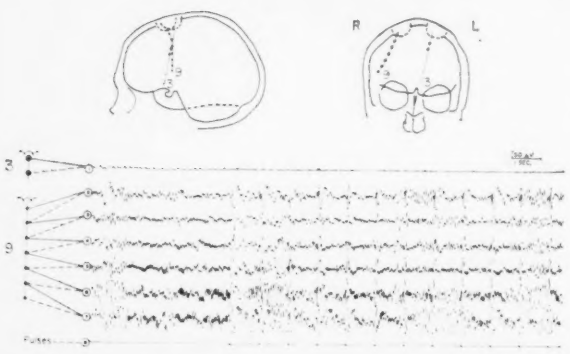

Fig. 2. Responses from lead 9 to stimulation with 1 pulse-pair per second of two adjacent electrodes on lead 3 (22.5 v. peak; 10 ma. peak). The appearance of 12 cycle-per-second sleep spindles partially masks some of these responses. Time constant: 0.125 sec. This and the following tracings were obtained preceding prefrontal lobotomy from a patient suffering from schizophrenic reaction, catatonic type.

The shape and complexity of the responses appeared to be related not infrequently to the characteristics of the background activity of the responsive cerebral area. For instance, a region showing fast background activity was more likely to respond with a multiple spike, whereas a region showing slow activity was more likely to exhibit responses including slow components—for instance, spike-and-wave complexes.

On the contrary, no constant relationship was found between the amplitude of the responses and that of the spontaneous background activity. Apart from some momentary variations in amplitude, the response in a given region tended to remain essentially unchanged so long as the parameters of stimulation were kept constant. Increase of the stimulatory voltage often resulted in an increase of the amplitude and sometimes of the complexity and duration of the response. It was found also that there was no relationship between the voltage of the responses from various regions and the distance of those regions from the stimulating electrodes. Conspicuous responses could be recorded from distant regions of the same or of the opposite hemisphere while electrodes located at a distance of 1 cm. from the stimulated point were totally unresponsive.

Sections A and B of Figure 3 show oscillographic recordings of interhemispheric responses to stimulation with one pulse-pair per second. These responses consist of biphasic (section A) or multiphasic (section B) potential variations, initially surface-pos-

itive, which because of electrode asymmetry often are obtained from heterotopic regions. When stimulation from a pair of electrodes located in one hemisphere provoked conspicuous responses that were recorded from an electrode pair located in the opposite hemisphere, stimulation of the latter electrodes with the same amount of current usually did not provoke any relevant responses recordable from the former.

Stimulation with three pulse-pairs per second (Fig. 4) could provoke in limited regions of the same or opposite hemispheres, or both, responses resembling the 3-per-second spike-and-wave complexes recorded over all head regions of epileptic patients during petit mal seizures (section A) or a variety of other spike-and-wave patterns (sections B and C). The most typical 3-per-second spike-and-waves were recorded from electrodes located in or close to the cortex.

Stimulation with 12 pulse-pairs per second provoked either of two types of responses: 1. A response consisting of simple biphasic oscillations at a frequency higher than and apparently harmonically related to that of the stimulation (Fig. 5, section A). This type of response usually was obtained from cerebral regions that show a fast background activity at rest, and thus it had the appearance of a marked voltage increase of such background activity with stimulation. 2. A succession of 12-per-second biphasic or multiphasic potentials that often showed an increment in amplitude with the first five-eight pulses and then waxed and waned to a variable extent (Fig. 3, section C, and Fig. 5, section B). This type of response was obtained also—and often more easily—during light and moderately deep (spontaneous) sleep (Fig. 5, section C). Such a recruiting type of response occasionally resulted in induced alpha-like rhythms involving wide cerebral regions (Fig. 6). In some observations a recruiting type of response limited to a given cerebral region evolved gradually into a self-sustained discharge that outlasted the stimulation period of 2 to 15 seconds (Fig. 7). In only one observation the afterdischarge spread further, leading to a generalized convulsive pattern.

The optimal stimulation rate was found to

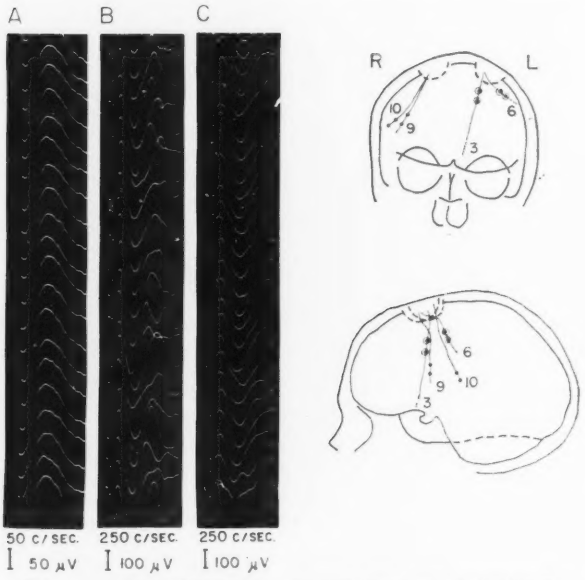

Fig. 3. Oscillographic recordings of interhemispheric responses. Section A: Responses from lead 10 to stimulation with 1 pulse-pair per second of two adjacent electrodes on lead 6 (27.5 v. peak; 10 ma. peak). Sections B and C: Responses from lead 9 to stimulation with 1 pulse-pair per second (section B) and with 12 pulse-pairs per second (section C) of adjacent electrodes on lead 3 (25 v. peak; 10 ma. peak). Negativity upward.

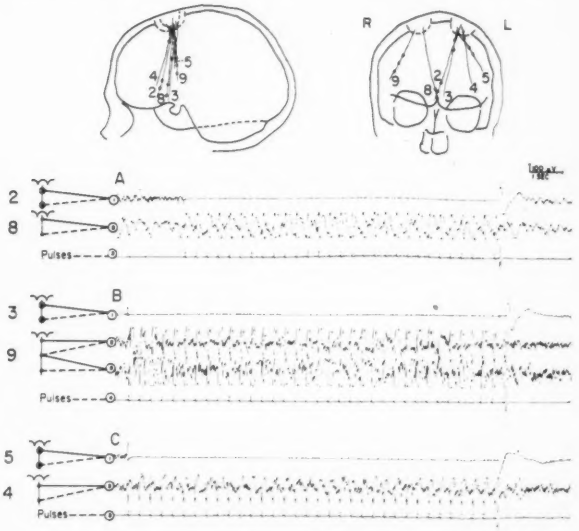

Fig. 4. Responses to stimulation with 3 pulse-pairs per second. Section A: Stimulation of electrodes on lead 2, recording from electrodes on lead 8 (37.5 v. peak; 10 ma. peak). Patient asleep. Section B: Stimulation of electrodes on lead 3 and recording from lead 9 (22.5 v. peak; 10 ma. peak). Patient asleep. Section C: Stimulation of electrodes on lead 5 and recording from lead 4 (30 v. peak; 10 ma. peak). Patient awake. In each section the decay-time constant was 0.033 sec. in channel 1 and 0.125 sec. in the others.

vary considerably from one cerebral region to the other. For instance, high-voltage responses could be obtained with 12 pulse-pairs per second from regions that gave only irrelevant responses to one pulse-pair per second.

Apart from the abovementioned convulsive seizure, no detectable objective changes were observed or subjective symptoms reported with this type of stimulation. The behavior and the state of consciousness of the patients appeared to be unaltered.

An incidental finding of some interest is that the interelectrode impedance was not significantly affected by stimulation with the short biphasic pulses. The same observation was made with stimulation of the electrodes in a 0.9 per cent saline solution. On the contrary, with the use of monophasic square waves in both saline solution and the brain, dramatic drops of the impedance values were encountered, suggesting the occurrence of changes that could result in injury to the brain tissue.

Comment

The characteristics of the responses recorded from various cortical and subcortical regions upon stimulation of the same and of the opposite hemisphere via a pair of intracerebral electrodes do not suggest simple spread of current through the tissue surrounding the stimulating electrodes. They appear to indicate the existence of neuronal connections between stimulated and responsive regions. It must be recognized that often an analysis of the intimate nature of these responses presents considerable difficulties. Indeed, it may be hard to determine whether the responses recorded in some observations are due to stimulation of gray matter or of fiber tracts, and to orthodromic or antidromic conduction along afferent or efferent or associative paths, or to the combination of several such effects. Despite

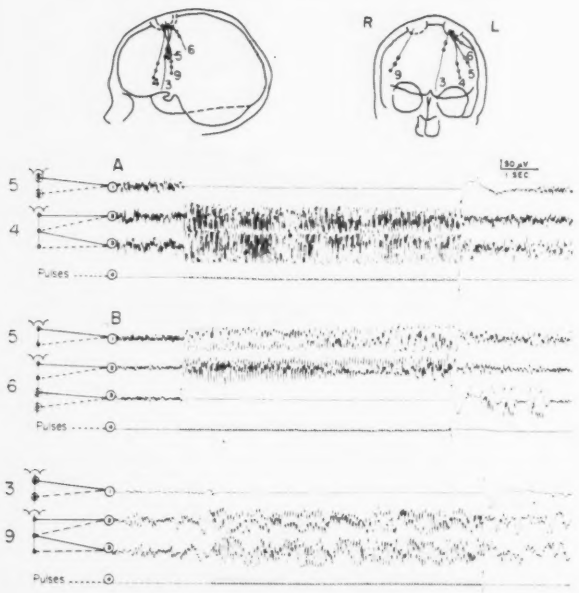

Fig. 5. Responses to stimulation with 12 pulse-pairs per second. Section A: Stimulation of electrodes on lead 5 and recording from lead 4 (37.5 v. peak; 10 ma. peak; 8 sec.). Time constant: 0.125 sec. Patient awake. Section B: Stimulation of electrodes on lead 6 and recording from leads 6 and 5 (27.5 v. peak; 10 ma. peak; 8 sec.). Time constant 0.033 sec. Patient awake. Section C: Stimulation of electrodes on lead 3, recording from lead 9 (22.5 v. peak; 10 ma. peak; 8 sec.). Time constant: 0.125 sec. Patient asleep.

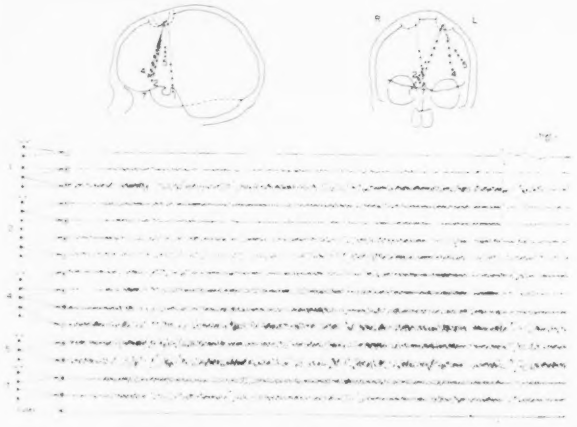

Fig. 6. Effects of stimulation with 12 pulse-pairs per second via two adjacent electrodes on lead 1 (27.5 v. peak; 10 ma. peak; 9.5 sec.). Time constant: 0.033 sec. Patient awake.

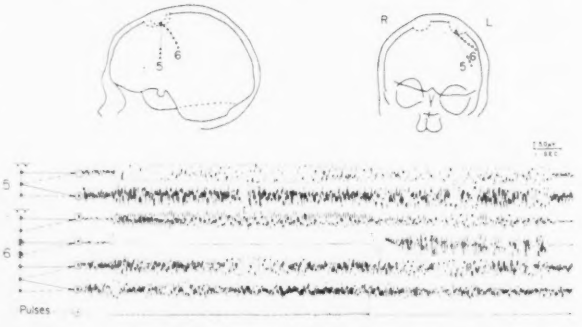

Fig. 7. Response to stimulation with 12 pulse-pairs per second of two adjacent electrodes on lead 1 (32.5 v. peak; 12.5 ma. peak; 19.5 sec.). Time constant: 0.033 sec. Light spontaneous sleep. Note evolution of response into self-sustained discharge.

these difficulties (which we plan to mitigate in the future by using a stereotaxic procedure for the implantation of the electrodes) the present findings give rise to interesting speculations.

Some interhemispheric responses bear considerable resemblance to the "callosal potentials" investigated in animals by Curtis and Bard,[9] Curtis,[10-12] McCulloch and Garol,[13] Chang,[14] Bremer,[15,16] and Peacock.[17] Whether or not mediated by callosal fibres (which could be ascertained only by section of the corpus callosum) these responses suggest the existence in the human brain of a wide system of commissural connections that probably play an important role in the mechanisms of higher cerebral integration (Bremer[16]). This system probably serves that incessant exchange of information between the two hemispheres which appears to be required for cerebral function in man.

The responses obtained upon stimulation with one pulse-pair per second are comparable to those observed by Bickford and associates[18] in man and by Spudis and Bickford[19] in animals. However, long-lasting disturbances of the type described by these authors have not been observed in our stimulations. This could be explained by their use of monophasic pulses of comparatively long duration.

That rhythmical spike-and-wave complexes may be recorded from limited regions of the cortex or its immediate vicinity as a response to 3-per-second stimulation of other cerebral regions in the same or opposite hemisphere of a nonepileptic subject is of some theoretical interest. This finding suggests that the cerebral cortex need not be in a state of abnormally increased excitability to respond with spike-and-waves to appropriate stimulation. Thus spike-and-waves may represent simply a mode of reaction of cell groups to direct or afferent stimulation common to both the epileptic and the nonepileptic brain. The observation may be considered as evidence that the recording of spike-and-wave complexes on the cortical surface in petit mal does not necessarily suggest that these waveforms are furnished as such to the cortex. This interpretation is in agreement with the views of Drooglever-Fortuyn.[20] Also, the finding that the most typical spike-and-wave patterns have been obtained from regions that before stimulation showed a slow background activity is in agreement with Droogleever-Fortuyn's opinion that in the production of spike-and-wave complexes two processes seem to interact: (1) the reaction of cell groups on a synchronous volley of impulses, (2) the preexisting rhythmic activity of the cortex. Finally, the recording of spike-and-wave responses from the brain of an adult patient suggests that incomplete cortical maturation is not an essential factor for the production of spike-and-wave discharges.

Another interesting feature is the responses to stimulation with 12 pulse-pairs per second, which vary from the exaggeration of local background rhythms to responses with recruiting features closely resembling spontaneous alpha rhythms and evolving (with adequate strength of stimulus) into self-sustained discharge. These observations provide some insight into the mechanisms of normal synchronization and of transition from normal to convulsive activity in the human brain.

Summary and Conclusions

Six hundred ninety-eight electrical stimulations of the brain with short biphasic pulses have been performed on two patients through electrodes implanted into the brain preceding surgical treatment. The results of these preliminary observations suggest that stimulation with single or repetitive pulses at low rates may provide valuable information as to: (1) the physiologic connections between various cerebral regions, (2) the transitional patterns from normal to convulsive activity and the mechanism of some epileptic patterns, (3) the pathways of spread within the human brain of convulsive discharges, and (4) the location of implanted electrodes.

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Adjunctive Therapy of Refractory Epilepsy with Prozine

PRISCILLA G. ILEM, M.D., and ROGER G. OSTERHELD, M.D.

Until recently, pharmacotherapy in epilepsy was directed solely toward reduction of the convulsive threshold. With the introduction of psychotherapeutic drugs, the correction of abnormal nervous impulses and the control of aberrant behavior became possible.

The anticonvulsant action of meprobamate was demonstrated by Berger.[1] Reports on the effectiveness of this drug in controlling epileptic seizures have been conflicting. Perlstein[2] reported improvement in 15 of 18 patients with idiopathic petit mal seizures. He considered the drug less effective in grand mal epilepsy; three of 14 patients were made worse by the treatment. Ivanov[3] observed an increased number of seizures in about one third of his patients, and he noted that the increased frequency was more common in petit mal seizures. Livingston[4] reported no significant improvement in patients with either type of epileptic seizure, but recommended meprobamate for the control of concurrent behavior difficulties.

In discussing one of his patients who had severe behavior disturbances, Ivanov suggested combined meprobamate-promazine therapy. A combination of these drugs, Prozine, has been used successfully in the treatment of psychosomatic disease.[5] This report compares the clinical responses observed when Prozine, promazine and chlorpromazine were used to treat epileptics who had severe behavior difficulties.

Details of Study

Prozine therapy was used for 12 male epileptics, ages 10 to 18 years. These patients were overactive, destructive and regressed. They had failed to respond to other tranquilizers, including chlorpromazine, prochlorperazine and reserpine. The duration of illness varied from six months to 18 years; in nine cases it was over ten years.

Complete physical and mental examinations were done prior to the study, and individual behavior problems were evaluated with ward employees. Other tranquilizers were discontinued three to four days before Prozine therapy was started. The patients were continued on their regular anticonvulsants. Eleven had been receiving various doses of phenobarbital, and one phenobarbital and diphenylhydantoin sodium. The starting dose of Prozine was determined on an individual basis according to the severity

of the symptoms. Each capsule contained meprobamate 200 mg., and promazine 25 mg. Five patients began with one capsule per day; the remaining seven patients were given two capsules per day. The dose was gradually increased until maximum effect was obtained or toxic reactions appeared.

After three months Prozine was discontinued and promazine therapy was substituted. The daily doses were determined on an individual basis; they varied from 150 to 400 mg. After two months, promazine therapy was interrupted and Prozine therapy reinstituted, using the optimal dose previously determined. Treatment was continued for another three months.

Hematological studies and urinalyses were performed before the study began, at various intervals during treatment, and at the end of the trial. Clinical progress, seizures, behavior and untoward effects were recorded daily. At the end of the trial, the clinical response was graded as follows: 0 no improvement; 1 slight improvement; 2 considerable improvement; and 3 remarkable improvement.

A concurrent study was made to determine the clinical effectiveness of chlorpromazine in a similar group of 12 younger male epileptics. The daily dose of this drug varied from 100 to 300 mg., depending on the tolerance of the individual patient. Treatment was continued for eight months.

Results

The clinical responses seen in our study are recorded in Table I. It is apparent that Prozine was the most effective of the drugs used. Improvement was considered remarkable in four cases. Three of these patients had idiopathic epilepsy; the other had epilepsy associated with congenital, traumatic brain injury. Anxiety, restlessness, destructiveness, temper tantrums, crying spells and unnecessary noisiness were greatly reduced or eliminated. All of these patients were mentally retarded; they had resisted efforts to care for them. During Prozine therapy they became alert, interested in their surroundings and cooperative. Their physical condition improved; weight increases varying from 1½ to 6 pounds, were recorded.

TABLE I

Clinical Effectiveness of Prozine, Promazine and Chlorpromazine in Refractory Cases of Epilepsy

Drug	No. of Patients	Degree of Clinical Improvement*			
		0	1	2	3
Prozine	12	3	3	2	4
Promazine	12	12	0	0	0
Chlorpromazine	12	12	0	0	0

*0—no improvement; 1—slight improvement; 2—considerable improvement; 3—remarkable improvement.

Improvement was good in two other patients with idiopathic epilepsy. These mentally retarded patients became more alert and cooperative; their aberrant behavior became less marked; crying spells, head banging and destructive episodes were reduced. Among the behavior abnormalities of one patient was a troublesome attitude at meal times, when he stole food and annoyed other patients. This behavior was controlled with Prozine and he lost three pounds.

Three patients were slightly improved. One of these had suffered from idiopathic epilepsy for 17 years. At the start of therapy he constantly pounded his head, cried continuously, made unnecessary noises and was irritable and uncooperative. During Prozine therapy his pounding episodes occurred only occasionally, but there was little other evidence of mental improvement. He did show considerable physical improvement. His appetite improved and he gained four pounds.

Two patients continued to improve slowly throughout the trial and prolonged therapy was recommended with reevaluation at a later date. Epilepsy was associated with brain damage following lead encephalitis in one of these patients. He continued to be a ward problem, but he developed periodic cooperativeness. His temper tantrums and masturbation were eliminated but his general behavior remained poor. He became more responsive emotionally and he gained 3½ pounds. The third patient had brain damage associated with congenital disease. Before treatment he was noisy, abusive, destructive

and unmanageable; he had severe head banging habits and suffered from insomnia. During Prozine therapy his general behavior improved slightly; his sleeping habits returned to normal and he was more cooperative.

The remaining three patients were unimproved, even with large doses of Prozine; the final daily doses were 2.9, 2.9 and 3.6 gm. None of these patients had idiopathic epilepsy. One had brain damage resulting from measles encephalitis; in the two other cases brain damage was associated with congenital disease. One of these patients had a decrease in the number of seizures, but his general behavior remained unchanged.

The effect of Prozine on the frequency of epileptic seizures is summarized in Table II. The seizures of nine of the 12 patients were controlled with anticonvulsants before Prozine therapy began. These patients continued to remain seizure-free throughout the study. Two patients had marked reductions in the number of seizures. In one case there was no significant change. The seizures in this case began after measles encephalitis, six months before this study started.

TABLE II

Effect of Prozine on Number of Epileptic Seizures

No. of Patients	NUMBER OF SEIZURES	
	In Three Months Preceding Trial	In Six Months of Prozine Therapy
9	0	0
1	7G*	1P*
1	6G	1G
1	1G	3G

*G=Grand-mal seizures; P=Petit-mal seizures.

The daily doses of Prozine required for maximum therapeutic effect are shown in Table III. No serious side effects were encountered during this trial. Nausea and vomiting were noted in two cases. In one the effect was transient; this patient was receiving a daily dose of 900 mg. In the other case, nausea and vomiting were overcome by reducing the daily dose and then increasing it gradually to 2900 mg. There were no laboratory findings indicative of drug toxicity. In particular, there were no significant decreases in the total white counts, and the differential counts remained within normal limits.

TABLE III

Optimal Daily Doses of Prozine

Number of Patients	Daily Dose* (mg.)	Response
1	450	Remarkable
2	675	
1	900	
1	450	Considerable
1	675	
2	675	Slight
1	900	

*Each 225 mg. capsule contained meprobamate, 200 mg.; and promazine 25 mg.

When these patients were changed to promazine therapy, they reverted to their original behavior conditions. Within four days the transformation was complete; the ward became noisy and unmanageable. Efforts to increase promazine to a therapeutically effective level were unsuccessful. In all cases severe drowsiness was noted before a therapeutic level was reached. Potentiation of the hypnotic action of phenobarbital may have contributed to this effect. The doses which caused drowsiness are recorded in Table IV.

Chlorpromazine was ineffective in all 12 cases. Diverse toxic manifestations were encountered; these included: drooling, drowsiness, dryness of the mucous membranes, nasopharyngeal inflammation and ataxia. The daily doses at which toxicity was noted are recorded in Table IV. Again, it should be noted that these doses were given in addition to the regular anticonvulsant doses of phenobarbital. These patients were continued on subtoxic doses for eight months without beneficial effect.

Discussion

In evaluating the foregoing data, it should be remembered that selected refractory groups were studied. The failures of chlorpromazine and promazine must be considered in this light. Both of these drugs have been used successfully in the management of behavior problems in epileptics. The outstand-

TABLE IV

*Daily Doses of Promazine and Chlorpromazine Producing Undesirable Side Effects**

Drug	Number of Patients	Daily Dose (mg.)
Chlorpromazine	1	150
	6	200
	2	300
	3	400
Promazine	3	200
	4	300
	5	600

*These doses were given in addition to regular anticonvulsant therapy.

ing results with Prozine assume greater significance because of the nature of the group examined.

The authors' previous experiences have confirmed published reports concerning the variable effectiveness of meprobamate in the treatment of epilepsy. The results with Prozine were superior. It appears that the small amount of promazine included in the preparation exerts a synergistic effect on the meprobamate. Continuation of previous anticonvulsant therapy probably contributed to the outstanding results.

The low incidence of side effects during Prozine therapy is encouraging. Nausea and vomiting were noted in two cases. In one of these, only one episode occurred; in the other, nausea and vomiting were overcome by reducing dosage and then slowly increasing it again. The results suggest that therapeutic doses of Prozine may be administered for prolonged periods without serious adverse side effects. In spite of this, strict medical supervision is recommended; individual side effects from prolonged therapy cannot be predicted from this small series.

Six of the patients treated with Prozine, had idiopathic epilepsy. Three of these had remarkable improvement; two, considerable improvement; and one, slight improvement. Thus, the results indicate that Prozine is particularly useful in the treatment of refractory cases of idiopathic epilepsy.

Summary

1. Twelve male epileptics, who had failed to respond to other tranquilizers, were treated with Prozine. The response was remarkable in four cases; good, in two cases; slight in three cases; and poor in three cases.

2. There was some improvement in six patients who had idiopathic epilepsy.

3. None of the patients in this group were improved by treatment with promazine.

4. None of the patients in a similar group were improved by chlorpromazine.

5. No serious side effects were observed during Prozine therapy.

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Authors' Note: The drug Prozine (200 mg. meprobamate, 25 mg. promazine hydrochloride) was supplied by Wyeth Laboratories, Philadelphia, Pa.

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Response of Chronic Schizophrenics to a Monoamine Oxidase Inhibitor

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In the past decade many new drugs have been marketed that appear to be beneficial in the treatment of psychiatric symptoms. The most prominent of these, the tranquilizers, are directed toward reducing anxiety and tension, and as such, are of limited value to many of our chronic schizophrenics. These patients are not responsive to either intrapsychic or environmental stimuli and would seem to require stimulation rather than tranquilization.

A class of drugs, described as "psychic energizers," and which provide symptomatic relief of depression, behave pharmacologically as monoamine oxidase inhibitors. In the hope that a psychic disinhibition effect would occur in our chronic schizophrenics, we decided to investigate one of these drugs, namely Marplan. With the exception of Hoshino and Cease's study,[1] which yielded negative results, other investigations of the effects of these drugs on chronic schizophrenics[2-5] had serious methodological flaws. Darling *et al.*[4] subjectively noted "improvement" under Marplan therapy for a group of chronic schizophrenics. Their findings need to be verified in a design employing controls and objective indication of behavior change.

Chronic male schizophrenics from closed wards were screened to locate those not receiving medication. This selection insured a predominance of passive, withdrawn patients who seldom create the sort of disturbance that results in the prescription of a tranquilizer or sedative. Of 600 patients surveyed, only 48 were not on medication and, in addition, met the following criteria as suitable subjects for the study: (a) under 60, (b) not lobotomized, (c) no convulsions or evidence of organic brain disease. A double-blind, cross-over design was employed so that each S served four weeks as an experimental S and four weeks as a control on inert placebo. A two-week interval on placebos was introduced between the experimental periods to permit S's to return to a physiological base.

From the Veterans Administration Hospital, Knoxville, Iowa.

The drug was administered for 28 days, according to the following schedule: 10 mg. each day for the first three days, 20 mg. each day for the next three days, 30 mg. for the subsequent 15 days, and 20 mg. for the last seven days.

Changes in behavioral adjustment on the ward were regarded as essential criteria for assessing the value of the investigatory drug for these patients. The Activity Rating Scale[6] (ARS) evaluates ward adjustment in terms of six-factor analytically derived dimensions.[7] Ratings of behavior were made by nursing assistants (attendants) who were in regular contact with the S's. Ratings were made independently by a day and an evening man. Whenever possible the original rater made the re-ratings at the end of the first experimental period and again at the end of the second. When a different rater did the re-rating, the change score was not included in any of the calculations. Of the 48 patients the data from only 38 on drug and 39 on placebo entered the calculations.

Raters were informed as to the general design of the study and that placebos were being employed. However, neither staff nor personnel knew the nature of the drug or what effects might be expected.[8] Raters were asked to consider only behavior during the last half of the drug-administration period, giving proportionally greater weight to most recent behavior. The raters were very conscientious as seen by the rate-rerate agreement, with correlations ranging from .65 to .85 on the six ARS scales. Change scores were calculated by subtracting the raw scores on the second rating from the first

rating, and by subtracting the third from the second rating.

Liver function tests were performed every two weeks. Three S's were dropped because their bromsulphalein retention after 30 minutes rose to between 10 and 14 per cent, although there were no prominent clinical symptoms observed. All three S's showed bromsulphalein retention within normal limits (less than 5 per cent) less than two weeks after discontinuance of the drug.

Mean change scores were not appreciably different while the S's were receiving the drug from those when on placebo. An analysis of variance failed to reveal any differences between the treatment and control periods significant at even the five per cent level of confidence; therefore, these differences are presumed to have occurred by chance and are not reported here. Side effects were never reported for any cases.

Second Study

Since our preliminary study failed to confirm Darling's findings, we were determined to see if this was because we had used half the daily dosage and administered the drug for only half the duration in his study.

The same subjects who served in the preliminary study were used again. For convenience we dropped a few subjects so that the remaining ones were located in only two buildings. Hospital diagnoses were: 11 hebephrenic, 9 chronic undifferentiated, 4 catatonic, 3 paranoid, and 2 simple type schizophrenic.

Marplan was administered for 56 days: 30 mg. per day for the first week and 60 mg. per day thereafter. Liver function tests (total bilirubin) were made each two weeks and were negative throughout. One S developed orthostatic hypotension severe enough to cause repeated fainting after four weeks of medication. Reduction of the daily dose to 30 mg. eliminated the fainting.

As before, the Activity Rating Scale evaluations were made independently for each subject by a day and an evening nursing assistant. Ratings made during the earlier study provided a control base-line, and the same rater's evaluation after two months of medication made it possible to calculate a simple change score.

Results are expressed in change scores, calculated by subtracting the average score on previous ratings from the present post-drug ratings. The previous ratings may have been slightly elevated by the earlier, smaller-dose drug administration although not to the degree that a real difference between drug and placebo ratings was detectable. Drug contamination of these ratings used for a base would tend to reduce the size of the difference scores in this study, so one can place even greater confidence in the reliability of any statistically significant changes found in difference scores.

The raters were informed as to the general aims of the study but were told that half of the subjects were receiving placebos. This deception was necessary to preserve the same set in the raters during the final rating period as existed at the time of earlier ratings during the first study. However, as before, the raters did not know the nature of the drug or what effects might be expected.

Results

Change scores, seen in Table I, reveal elevation on four factors: Deteriorated Behavior, Emotional Controls, Resistive Isolation, and Regressive Activity.

The probability values, *p*, in Table I indicate that the Deteriorated Behavior, Emotional Controls, and Regressive Activity scales were significantly elevated. A fourth scale, Resistive Isolation, is also elevated but that amount of elevation could easily have

TABLE I

Mean Raw Scores and Change Scores for Activity Rating Scale

	FACTORS					
	Deterior. Behavior	Interper. Tension	Emotion. Controls	Resistive Isolation	Regress. Activity	Reality Conctrn
Post Drug	13.90	14.55	12.38	15.28	16.66	18.46
Pre-Drug Base	12.76	14.46	11.78	14.57	16.11	18.46
Change Score	1.14	.09	.60	.71	.55	.00
t-test	4.45		3.65	2.20	2.53	
p	.01		.001	.10	.05	

occurred by chance alone. Thus, only Interpersonal Tensions and Reality Concern clearly remain unmodified by the administration of heavy doses of Marplan.

Since the rater's set and instructions were exactly the same as in the preliminary study, the only difference in experimental conditions was the heavy and prolonged drug dosage and a two-month interval between ratings. An analysis of earlier ratings, separated by two and a half months, was not appreciably different from those made a month apart with two exceptions. The Deteriorated Behavior mean change score was .25 greater for the longer interval, and the Resistive Isolation mean change score was .18 greater. Subtracting these amounts from the change scores for the respective factors in Table I gives the p values seen in that table. Thus, the reported p values are larger than when calculated without this correction for time lapse between ratings and do not correspond with the reported t's for the two factors.

Discussion

The psychiatrist, who hopes to see chronic schizophrenics blossom into healthy, socially oriented responsiveness, will be disappointed by these results. It is apparent that Marplan does not produce socially constructive, reality-oriented responses, or inhibit personalistic, schizophrenic displays. The psychiatrist, who views any change in an anergic, chronic schizophrenic as increasing accessibility for therapeutic interaction, may wish to investigate the use of Marplan as the first step in an active therapeutic attack on a chronic schizophrenic disorder.

Individual patients manifest great variability on their change scores. One will show a marked change on only one scale, some on several scales, while others show no changes at all. Despite moderate intercorrelations between the raw scores on the three significantly elevated scales, no trace of intercorrelation is found among change scores for these scales.

Only four patients showed a negative average change score for the three relevant scales with a range of —.29 to —.02. These are low and occur infrequently enough to be ascribed to chance. We conclude that patients such as those in our sample either change in the expected direction or do not change at all.

The question arises as to whether or not the initial level of behavioral adjustment can be used to show which patients will show the most change under Marplan. Correlational analyses of our data lead us to conclude that there is no relationship between the nature of ward adjustment and response to Marplan.

Since it was apparent that some subjects showed appreciable change while others did not, it would be interesting to see whether the two building nurses could agree with the ratings made by nursing assistants. The 13 patients of the 29 who were believed by the nurses to have shown change under medication have an average change score for each of the three relevant scales of 1.03. The remaining 16 patients show an average change score of only .52. The correspondence between the average change on the three Activity Rating Scale scores and the nurses' judgments is striking. It is clear that the amount of change shown by some subjects is large enough to be of clinical significance and is not just a minor change identifiable only through careful measurement. Thus, our results confirm the findings of Darling, although we would avoid the value judgment of placing the subjects in an "improved-worsened" frame of reference.

Authors' Note: Marplan used in this study is the tradename of the compound isocarboxazid (Ro 5-0831/1) supplied by Hoffmann-La Roche Inc., Nutley, N. J.

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Oculogyric Crisis Induced by Phenothiazine Drugs

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An oculogyric crisis consists of a spasmodic conjugate deviation of the eyes usually upward and outward with retraction of the lids and an associated deviation of the head in the same direction. Torticollis and opisthotonus may occur and respiratory difficulty may be encountered. This condition has previously been associated with post-encephalitic parkinsonism.[1] The authors have, between them, observed seven cases of oculogyric crisis occurring in patients who were receiving phenothiazine drugs.

Case 1. B.B.S. is a 31 year old registered nurse who was admitted because of drug addiction to demerol. By the day after admission she had received a total of Thorazine (chlorpromazine) 600 mg. in divided doses, and Dilantin 1½ gr. t.i.d. That day she was seen sitting in bed, frightened to death, unable to speak because of air hunger, very pale with slightly blue lips and fingernails. The tongue showed edema especially under the tip, with a slightly bluish discoloration. Pulse was rapid but good.

The patient was placed in an oxygen tent and the air hunger disappeared within ten minutes. About 10-15 minutes later an acute and very severe oculogyric crisis occurred with attacks of apparently torturing opisthotonus every two to three minutes, each lasting 2-5 minutes. The patient was evidently in much pain.

She was given atropine grains one fiftieth subcutaneously twice and 2 cc. of Benadryl slowly intravenously. The attacks gradually became slighter and less frequent and subsided entirely within a half hour.

Case 2. R.S., a 26 year old white male, was receiving Thorazine for paranoid schizophrenia of long standing, and had had it frequently before in doses up to 100 mgm. q.i.d. On March 22, 1957 he took Thorazine 300 mgm. at 8:00 A.M. and by the afternoon developed a typical oculogyric crisis with opisthotonus and some difficulty with respiration. Throughout the day he continued to have the eye signs. He was very restless and unable to lie down. His breathing continued to be difficult and he had chest pains. He was treated with Pyribenzamine and Pipanol and after 12 hours his condition improved. He has since had Thorazine in smaller doses (up to 50 mgm. t.i.d.) without any untoward reactions.

Case 3. M.V., an 18 year old white male who is being treated with insulin coma therapy for paranoid schizophrenia. He received Stelazine (trifluoperazine dihydrochloride) 20 mgm. a day in divided doses for three days. It was reported that the patient had jumped over a tennis net and hurt his back. When seen he showed marked opisthotonus with severe neck rigidity. His chin was turned to the left and his eyes upward and to the left. The patient was able to control this state for a few seconds at a time, but quickly reverted to the former position. The condition cleared up rapidly when the Stelazine was discontinued and Pipanol was given.

Case 4. C.F., a 23 year old female paranoid schizophrenic, was on Trilafon 4 mgm. at bedtime. One night, while on visit, she took Trilafon 24 mgm. and 8 mgm. at 11:00 A.M. the next morning. That day at 2:30 P.M. she developed a typical oculogyric crisis with opisthotonus. This lasted one half hour and was treated with Benadryl 2 cc. subcutaneously.

Four months later she was taking Trilafon 2 mgm. b.i.d. without ill effects.

Case 5. D.L.H., a mentally defective child, showed a speech disorder, assaultiveness, and was incontinent. He was on Thorazine 50 mgm. q.i.d. He developed an oculogyric crisis characterized by opisthotonus, torticollis, and his eyes rolled upward. He was able to control this to some extent. The mother reported a similar attack one year previously also while on Thorazine. He is still taking the same drug and the same dose without further attacks.

Case 6. R.N., an 18 year old manic who was taking Dilantin 1½ gr. b.i.d. for major seizures of unidentified origin, had been taking Thorazine 100 mgm. t.i.d. for some months. He developed an oculogyric crisis after taking his full daily dose (300 mgm.) by mistake all at once. The drug was discontinued and after a brief period was resumed without further attacks.

Case 7. R.R., a 22 year old mental defective youth had been receiving Thorazine 200 mgm. b.i.d. for 3 years. When the dosage was increased to 200 mgm. t.i.d. because of hyperactivity, he developed the same pattern as heretofore described. After treatment with Pipanol and Benadryl the crisis cleared. He has been able to take the former dosage without recurrence.

Discussion

In the cases described oculogyric crises occurred in the absence of any history of encephalitis and of the other signs of parkinsonism which may accompany medication with the phenothiazine drugs.

Brock has stated: "In cases of epidemic encephalitis, the clinician encounters patients who suffer from sustained spasms of tonic conjugate deviation of the eyes.

The commonest variety is an upward fixation of the eyeballs. These 'ceiling spasms' are sometimes maintained for hours after which the eyes return to their normal position. These oculogyric crises may be associated with states of anxiety, compulsions, phobias, fatigability and weakness of will, all of which suggest the participation of cerebral factors. Riley believes that both cortical and striatal disease is responsible for their occurrence. Muskens attributes these crises to disease of the supravestibular pathway. Aside from nystagmus, extrapyramidal involuntary movements of ocular muscles are not common, though their existence proves that the basal ganglia participate in the innervation of the ocular muscles."[2]

Ayd,[3] in a review of the physiological and neurological action of chlorpromazine says: "The clinical observation that in therapeutic doses chlorpromazine suppresses the tremors and involuntary movements of various extrapyramidal syndromes, while in larger doses this drug may cause the appearance of an extrapyramidal disorder (paralysis agitans), is consistent with the experimental work cited above which shows that chlorpromazine in small doses suppresses the reticular formation, whereas larger doses stimulate the reticular formation."

Six of our patients developed the syndrome either soon after the initiation of treatment or after receiving a higher dose than usual.

Beside the therapeutic effects as such, the neurological side effects of the phenothiazine drugs are symptomatically similar to the after effects of encephalitis, and include rigidity, tremor, mask-like facies, drooling, inner restlessness, excitement, oculogyric crises, and epileptiform convulsions. It is essential to be aware of these side effects, particularly for the treatment of patients on an out-patient basis.[4-8]

The phenomena described in this paper although in themselves involuntary, can occasionally be influenced by conscious control or by suggestion. However, the effect is not lasting, and may be likened to the temporary improvement of parkinsonian tremor by hypnosis. This may lead one to suspect falsely that one deals with an hysterical patient. It is sufficiently established that these disturbances of kinesis are not based on psychodynamic mechanisms.

The attacks are dramatic and frightening, and have so far not recurred under our own observation. There appears no reason to discontinue the respective phenothiazine preparation, unless the crises appear repeatedly. It must be borne in mind that a sudden increase in the dose in relation to the patient may precipitate an attack.

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Emotional Content, Extraversion, and Aptitude, in Man

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Introduction

The following concept stimulated the clinical investigation and conclusions in this paper.

"All persons, due to inherent emotional content, show emotional spontaneity or extraversion, but in different degrees."

In 1942 I was accepted as a medical officer in the U.S.N.R. and I served on active duty for over three years. Two of these three years were spent as a psychiatric examiner and consultant in one of the largest Armed Forces Induction and Recruiting Centers in the Southwest. Thousands of males between 18 and 36 years were processed yearly. This assignment was ideal for collecting clinical data relative to man's degree of emotional content, and capacity of emotion, termed, emotivity, as well as his emotional spontaneity or extraversion. I found that the higher the degree of emotional capacity—emotivity, the higher the degree of emotional spontaneity or extraversion.

After two years, I was satisfied professionally that the preceding concept was sound as well as correct. Having used this material daily during the past seventeen years, I am certain in my mind that this information is scientifically and clinically correct, as well as helpful personally and professionally.

The purpose of this paper is to attempt to present three additional concepts that may aid in a more adequate evaluation of oneself and others as to the normal level or degree of emotional content, capacity, or emotivity giving rise to emotional spontaneity or extraversion. "Extraversion or extroverted" are used in this paper to mean emotional outgoingness or emotional spontaneity.

An individual's emotional content, capacity, or emotivity and extraversion (which normally parallels emotivity) springs basically from his constitutional make-up—from the soma or body, not the psyche. Emotivity and emotional spontaneity or extraversion are normally present in all persons in different degree. Emotivity and extraversion basically have nothing in common with body build, its shape, form, or type;[1] nor with the words "extrovert" and "introvert" as nouns.[2] Secondly, in every marriage each party normally shows extraversion, each is extroverted, but one is normally higher on the "Scale of Emotional Spontaneity or Extraversion" and has different aptitudes. Thirdly, aptitude, not interest, developes from the emotions or feelings, which in turn arise from the body and brain, including its physiological and biochemical activity, not the intellect or mind.

Emotional Content of Persons—Mote and Exmote

The writer has coined the words, "Mote and Exmote" to describe and differentiate individuals on the basis of emotional content and capacity. It is my belief that emotions and emotional capacity are totally biologic in nature. They evolve from the structural and physiological constituents of the person—from the soma, not the psyche.

The words, Mote and Exmote, describes emotional potentialities normal to its own classification or group. They are derived from the Latin word *emotus,* the past participle of *emoveo*—meaning, move outward. "Emotion" has its origin in this same root. The prefix "ex" denotes an individual, a person whose emotional content, capacity, and emotivity is, from birth, normally greater than that of a "Mote." The Exmote is so constituted that his physical apparatus, physiology and chemistry, make it possible for him to experience emotion and express more readily or spontaneously. Due to this constitutional factor he, therefore, has a higher level of emotional content, capacity, or emotivity; a greater degree of emotional expression; and normally, he is more highly extraverted than a Mote.

An individual at birth, because of these basic factors, normally possesses a constitu-

tion which is physically or biologically greater, equal, or lesser in emotional capacity, or emotivity than another individual. Change in the degree of emotivity, spontaneity, or extraversion may be felt subjectively or observed objectively by others in his immediate environment. Such a condition is a common symptom in physical fatigue or depressive states although no organic or structural alterations have taken place. The change that is felt or seen takes place within the total functional apparatus—including the physiology, biochemistry, and psychology or mental system. Such a finding or condition at one time was referred to as a "functional disorder." Now it is more properly looked upon as a psychosomatic or psychophysiologic disorder. The latter terms embrace *all* body functions, and all emotional-mental functions of the total person.

A person may, and can have a marked alteration in his normal body and mind activity, but his basic physical structure (when no organic disease is present) remains the same. The constitution termed the "Exmote" can never become that of the Mote or vice versa, regardless of depression, introversion, or introspection. A person can, because of such a psychosomatic condition become less extroverted, and show less emotional enthusiasm, spontaneity or extroversion, and become more introspective or intraverted than normally. Such intrapersonal changes are usually temporary and with proper treatment readily reversible.

Either constitution, Mote or Exmote, can be victims of emotional-mental conflicts (intrapersonal), which in time may lead to a more or less serious psychosomatic condition evidenced in a variety of ways, including fatigue, depression, introversion, and introspection. This personality, at such a time, may be considered "intraverted." There are four factors that differentiate persons under the heading of Mote and Exmote: (1) degree of emotional content or emotivity; (2) emotional spontaneity; (3) level of extraversion; (4) personal aptitudes. The Exmote constitution places higher on the scale in all of the first three; the fourth—aptitude—also shows a basic difference.

Normally All Persons Show Extraversion

The constitutional make-up of both a Mote and Exmote normally shows extraversion but in a different degree. Therefore all persons by their physical nature and emotional content, not by psychological make-up, are extroverted or emotionally outgoing, *more* or *less*. However, the extroverted Mote normally will never reach the degree of extraversion of the extraverted Exmote, so because the emotional content of the physical constitution, termed the Mote, is naturally and normally in a lower register than the Exmote. (A drawing presenting a Scale of Emotional Spontaneity or Extraversion is shown in Figure 1.)

By using this information concerning constitutional make-up of persons, we may be able to correct misconceptions of persons, who, because of constitutional make-up are basically Motes, but have identified themselves as introverts instead of Motes.

Korzybski[3] describes the nouns, Extrovert and Introvert, most interestingly:

> "Aristotle (384-322 B.C.) was born in Stagira, Greece. He was the son of a physician and had marked predilection for natural history and a distinct dislike for mathematics. Plato, who is considered the father of mathematicians, was his teacher. Early in his career Aristotle reacted strongly against the mathematical philosophy of his teacher, and began to build up his own system, which had a strong biological bias and character. Psycho-logically, Aristotle was a typical extrovert, who projects all his internal processes on the outside world and objectifies them; so his reaction against Plato, the typical introvert, for whom reality was all inside, was a natural and rather an inevitable consequence."

This writer describes Aristotle as a typical Exmote, and Plato, as a typical Mote; both extroverted but in different degrees; both showing the aptitude normal to each—Aristotle being the more expansive, expressive, and extroverted; Plato the technician, was less expansive, expressive and less extroverted. He would place lower on the "Scale of Emotional Spontaneity or Extraversion" than Aristotle. The writer no longer uses the nouns extrovert or introvert.

The nouns—Mote and Exmote—are biologic. They are descriptive terms which im-

ply no psychological or personality reference. Every person born is naturally and normally one or the other. Conflict can arise within one, by not understanding it.

The word "introverted" is used by the writer to describe a pathologic condition. This takes place when the individual is suffering from an emotional-psychological state or condition, which may be associated with some degree of physical fatigue or depression. This same person, normally, or previously, could have been very high on the scale of emotivity and extraversion, and because of this could have been highly extroverted before his physical fatigue, introspection, anxiety, and lack of self-confidence developed.

A Mote and an Exmote in Every Marriage

During the seventeen years, in which I have been recording impressions concerning the two groups, the following and very interesting observations have been proven. These are most helpful, clinically and personally. They are also factual.

The majority (90%) of females have the constitutional, biological and emotional content or make-up of the Exmote; the majority (90%) of males, Motes. This finding has nothing to do with "sex" as such, nor has it anything in common with masculinity or femininity. A woman who is an Exmote is not an Exmote because she is a female; nor a man that is a Mote is not a Mote because he is a male. The Mote and Exmote have to do only with a basic and specific factor, the emotional content of the person; this is a constitutional factor, regardless of sex.

As a rule of thumb, however, the average male is a Mote; the average female, an Exmote. Ninety per cent of all marriages show an Exmote, wife, and a Mote, husband. In every marriage I have found "one Mote and one Exmote—one of each in every marriage." In short, all other things being equal, Mote and Exmote marry. There may be exceptions, but in this study I haven't encountered any. Normally both are extroverted or emotionally outgoing, but in different degrees; and often the difference in degree may be marked.

A misconception of this natural, normal attraction, the Exmote (+) and the Mote (—) coming together in marriage, results from a lack of specific knowledge and understanding. This natural attraction can become an unrecognized area of interpersonal conflict regardless of their conscious devotion to one another.

By the way of illustration, the following is presented:

Scales of Emotional Spontaneity or Extraversion in the Mote and Exmote

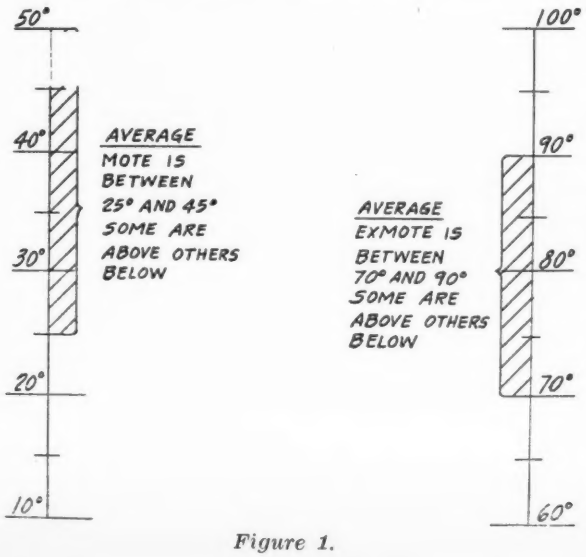

Figure 1.

A middle-aged man was referred because of gastro-intestinal symptoms. This condition was recognized after a thorough and complete examination by the clinician who diagnosed the case as "functional" or psychosomatic in nature. A complete study of the patient from the psychobiological approach was made emphasizing analytical psychotherapy. However, the author feels that much emotional-psychological traumata, or inner conflict, which constituted much of the psychopathology isolated during the process of psychotherapy could have been prevented, if this patient had been given a better understanding of his own and his wife's normal emotional capacities. The patient was a Mote, and his wife, an Exmote. By reason of the patient's lack of insight into this natural fact, a marked degree of conflict between husband and wife had developed during their married life.

The wife, an extroverted Exmote had been, throughout the years, attempting to change the patient's personality from what she termed an "introvert" into which she wanted him to be, an "extrovert." It was her conviction that anyone could,

if they so willed and tried, become an extrovert. If the belief were for one to become "extroverted," it would have an element of truth. However, this too would have limitations which the wife did not fully appreciate. Not because she wanted to be domineering, but rather because of her lack of understanding that physically and emotionally her husband was a Mote, slightly extroverted, and not an Exmote, markedly extroverted, as was she.

Her endeavors were sincere but unintelligent, and because of much interpersonal bickering, many emotional-psychological conflicts arose. Also due to the wife's emotional capacity and the facility with which she could emote and unintentionally "nag," the husband took the toll. With time this condition became aggravated and more and more emotional-mental conflict grew within the husband, resulting in excess emotional-mental tension or pressure to his total person—body and mind. Psychologically, instead of becoming what she wanted—an "extrovert"—he had, because of his ever-mounting emotional-psychological conflict, become more and more introspective and introverted.

Proper supportive measures in the form of materia medica, were prescribed. However, before this case could be concluded something more was needed—an interview with the patient's wife. She was pleased when she learned that the differences in emotional content, emotivity, and extroversion between her and her husband were normal.

In the above case, the same interpersonal difficulties would exist if the situation were reversed—the husband being an Exmote. He would try to persuade or change the wife, normally a Mote, to come up to, and to compete with his higher level of emotivity, spontaneity and extraversion. In either case, why should it be necessary to change that which is natural and normal? But "innocent ignorance," can cause a great deal of emotional-psychological harm or traumata. Such conflict, over a period of time, can lead to definite psychosomatic or psychophysiologic changes within the body and mind.

Aptitudes Mote and Exmote

Aptitude connotes a certain naturalness, an attraction, a feeling already existing within an individual which helps render an accomplishment the more readily attainable. It is my conclusion that aptitudes basically spring from the emotions, not the mind. It takes the mind to create the interest; the "will" to stay with one's interest. The Mote and the Exmote have aptitudes corresponding to their emotional constitutions. However, the Exmote has more aptitude for emotional spontaneity or extraversion; his gregariousness comes easier; it is more natural for him than for the Mote. The Mote, aptitude-wise, has other advantages in science, business and professional endeavors. It goes without saying that for success, all necessary factors must be present. These include, in part, intellectual capacity as well as desire, and the will to do, before a reasonable accomplishment may be achieved, whether the personality is basically a Mote or an Exmote.

Generalizations as to the aptitudes of the Mote and Exmote follow. These basic principles will help to formulate specific specialties, positions, or occupations. The Mote, because of his emotional component, has an aptitude for a more adequate adjustment, all other things being equal, for the following:

1. Any professional or non-professional occupation requiring a mechanical or technical trend including science.

2. Mathematical trends. (This is why the average female, an Exmote and non-technician, confuses the Mote educator.)

3. Executive ability, including all the technical ramifications normal to an executive, exclusive of continued gregariousness.

These generalizations reduced to specific occupations such as mathematician, physicist, musician, machine operator, statistician, engineer, surgeon, executive, photographer, tactician, chef, mechanic, professional golfer, to mention but a few, demonstrate that the aptitudes of the Mote exceed those of the Exmote.

The Exmote personality will encounter less emotional-psychological resistance or difficulty than the Mote, other things being equal, in pursuing an activity falling under these general headings:

1. History, people, contact work—in the social, business or professional fields.

2. Dramatics. (However, the average female actress is an Exmote; the average male actor is a Mote.)

The personalities that may be considered "natural" under the above categories for the Exmote are so because of their "emotional-

ity" or constitutional make-up in which a high degree of emotional content or emotivity is expressed. The "natural" salesman, organizer, promoter, or actor is usually an Exmote. In business or professional life this "natural" trend will be of advantage as long as a person remains in a sphere or field requiring his aptitudes. In the field of dramatics no doubt there are many successful personalities who are not Exmotes. However, such individuals, although successful and popular, are nevertheless, because of a lack of high emotivity, limited. And if this is not understood by the individual it could be the cause of much inner conflict. It is more difficult for the Mote constitution to play a variety of dramatic roles. If attempted, it would cost the Mote more in physical energy to show a high level of emotivity or emotionality than a person who constitutionally has more emotional capacity.

The majority of outstanding actresses must be described as extroverted Exmotes; a lesser number are extroverted Motes. All actors are extroverted, but unlike the actresses, most are Motes; a lesser number are Exmotes. Their aptitudes are less technical, they come under what is termed—expressiveness, outgoingness, and verbalization. It is easier or more natural for the Exmote to emote. Either the Exmote or Mote, depending upon the way they "feel" at a certain time and normally can slide several degrees up or down the Scale of Emotional Spontaneity or Extraversion.

I would like to amend the statement "opposites attract" to read "opposite aptitudes attract" which then gives the expression a specific meaning.

Examples of Males—Extroverted in Different Degrees

MOTES

Dwight Eisenhower	Bob Hope
Bernard Baruch	Winston Churchill
Bob Considine	Herbert Hoover
John Foster Dulles	Stalin
Franklin D. Roosevelt	Plato

Each Mote personality listed places somewhere between 10 and 50 degrees on the scale of emotional spontaneity or extraversion.

EXMOTES

Richard Nixon	Frank Sinatra
Harry Truman	Bishop Fulton Sheen
Jackie Gleason	Billy Graham
Wm. Hearst Jr.	Nikita Khruschev
Walter Winchell	Aristotle

Each Exmote personality listed places somewhere between 60 and 100 degrees on the scale of emotional spontaneity or extraversion.

(On the Scale of Emotional Spontaneity or Extraversion, the wife of the Mote is between 60 and 100 degrees; the wife of the Exmote is between 10 and 50 degrees.)

Summary

1. This paper holds that all persons are born extraverted, in different degrees. This is due to the person's biologic or constitutional make-up; not the psychologic.

2. After many years of research, the following conclusion has been reached: 90 per cent of males are classified under the Mote constitution as compared to 10 per cent of females. Ninety per cent of females are under Exmote constitution as compared to 10 per cent of males.

3. To identify these two groups—the more highly extraverted from the less extraverted—two nouns have been "coined," namely—*Mote* and *Exmote*. These words were suggested by the word emotion—to move out, from the Latin emotus, the p.p. of emoveo. These words replace the nouns extrovert and introvert but not the adjectives—extraverted or intraverted. Either the *Mote* or *Exmote* can become less extraverted because of physical fatigue.

4. Human aptitudes as well as extraversion spring basically from emotions or feelings. These are biologic and inherent at birth whereas interest comes from the mind.

5. Opposite aptitudes attract; all other things equal they marry. Every marriage consists of a *Mote* and *Exmote*.

6. The constitution termed the *Exmote* can never become a *Mote* or vice versa.

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A Symptomatic Analysis of the Effects of Perphenazine

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The ability of the pharmacologist to alter the structure of drugs, thereby producing new affects or increased therapeutic efficacy, has resulted in dramatic changes in medical therapeutics. One result of this ability has been the introduction into psychiatry of many "tranquilizing" drugs some of which have proved to have decreased toxicity and increased therapeutic efficacy. Early reports[1-6] concerning the use of the drug, perphenazine, indicated several advantages: a decreased hypotensive effect, decreased hepatic toxicity, and an apparently increased therapeutic efficacy and potency. This study attempts an evaluation of the drug beyond the scope of previous clinical investigations and to ascertain in what areas of symptomatology and behavior the drug is most effective. The data reported here represent the result of this attempt.

Patient Material and Method:

The 196 patients in this study were all adult male veterans (age range 20 to 72 years) who were admitted to the psychiatric service of the Veterans Administration Hospital in Durham, North Carolina. At the beginning of the study it was arranged that all patients for whom a tranquilizer was indicated would be placed on perphenazine. A one week period of administration of the drug was the minimum acceptable trial, except where side effects made discontinuance necessary. A routine series of laboratory procedures were carried out before the administation of the drug. These included an electroencephalogram, hematologic examination, and urinalysis. Liver function studies were the thymol turbidity and flocculation, as well as a B.S.P. when the physical examination or history indicated that it was necessary. Blood pressure was recorded twice daily in each patient. Hematologic, urine and liver studies were repeated at weekly intervals. Patients were observed for a minimum of three to four days after admission before therapy was begun except in a few cases of acute excitements and acute delirium tremens where the patient's welfare necessitated immediate administration.

Prior to the institution of therapy a standard evaluation form was filled out by the physician in charge of the case. The following symptomatological and behavioral data was recorded and graded as to severity on an 0 to 4+ basis:

A. Behavioral:
1) Agitated; 2) Combative; 3) Excited; 4) Tremulous; 5) Hyperactive; 6) Catatonic; 7) Hostile; 8) Other.

B. Speech:
1) Talkative; 2) Mute.

C. Mood:
1) Elated; 2) Depressed; 3) Anxiety.

D. Content:
1) Hallucinations—a. auditory, b. visual, c. other.
2) Delusions—a. persecutory, b. guilt, c. unworthy, d. somatic, e. grandeur, f. depersonalization.
3) Suicidal preoccupation.

E. Sensorium:
1) Orientation; 2) Memory; 3) Calculation.

Following termination of treatment or when a maximum therapeutic effect had been ascertained a second copy of the evaluation form was filled out. The data obtained was separated into diagnostic categories and the total number of patients in the group who showed a particular symptom or behavioral disturbance and the number showing a change of 2+ or more in this particular symptom or behavioral disturbance was recorded. Complete data was available on 184 patients.

Finally the overall effect of the drug was determined by the physician in charge. Any

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The drug, perphenazine, used in this study was supplied by Schering Corporation under their tradename Trilafon.

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side effects occurring during the course of treatment was recorded. Often resident physicians carried out evaluation of the patient and as a result occasional difficulty was encountered in uniformity of classifications into diagnostic categories; however, for the final analysis of the data the diagnoses as determined by one of the three authors were used since they had been involved in the supervision of the care of the patients and were personally acquainted with the patient.

For the purpose of clarity the following criteria were used for the various categories:

1. *Schizophrenia*—these patients were characterized by the basic symptomatology as described by Bleuler. The various types were determined by the predominant secondary symptomatology.

2. *Manic-depressive psychosis*—these patients had unequivocal evidence of a pervasive affective disorder with secondary biological concomitants, and a clear history of one or more previous attacks of manic or depressive symptoms.

3. *Psychotic depressive reaction*—these patients showed pervasive affective disturbances with associated biological concomitants of depression. No history of a previous attack could be elicited.

4. *Psychoneurotic disorder*—this diagnosis was limited to the less severe psychiatric syndromes as defined in the standard nomenclature. In most instances this group of patients had long histories of neurotic complaints and symptoms which seriously interfered with their everyday living.

5. *The acute brain syndromes* were limited to those patients with reversible recoverable delirium usually due to alcohol or drugs. In this study all of the patients had delirium tremens.

6. *Chronic brain syndromes*—this group of patients were for the most part patients with epilepsy but also contained a small number of patients with senile psychoses and arteriosclerotic cerebral vascular disease. The standard diagnostic criteria found in the "Diagnostic and Statistical Manual of Mental disorders"[1] were used.

Dosage:

All patients were routinely started on 4 mg. four times daily. This dosage was then increased in two days to 8 mg. if no clinical response was observed at the lower dosage. Subsequent dosage increases to 16 and 32 mg. q.i.d. were carried out if clinically indicated. Anti-Parkinson drugs were administered to control side effects. If the patient had shown no improvement in seven to ten days, the drug was considered to have no effect and other indicated therapies were then instituted. In some instances where moderate improvement was noted the drug was continued until further improvement was apparent, or it became obvious that no further change had occurred. If good relief of symptomatology was obtained the higher doses were gradually reduced and the patient maintained when possible on 4 to 8 mg. once or twice daily. This technique proved satisfactory in most instances. No other forms of therapy were administered during the course of therapy except in patients who had epilepsy and were receiving anticonvulsants, and those patients with delirium tremens who concomitantly received fluids, vitamins, and Dilantin. The latter was in anticipation of alcoholic withdrawal seizures.

Results

The data for diagnostic groupings (Table I) indicates that with the exception of patients with chronic brain syndromes, there was an adequate representation of the various diagnostic groups.

The general therapeutic results observed were encouraging (Table II); a profound reduction in the intensity of symptomatology, i.e. 50% or more, was observed in 42% of the patients. A complete remission of symptomatology was observed in only 22%; however, one-half of these were patients who had self-limiting diseases that carried a good prognosis for recovery irrespective of medication (acute brain syndromes). Indeed in those syndromes where the symptoms were not related to toxic or metabolic disorders the percentage of a complete remission of symptoms, was even lower, 7%. Nevertheless, the general reduction of symptomatol-

ogy observed in the entire series was sufficient to provoke favorable spontaneous comments from many of the personnel of the psychiatric service as to its obviously increased efficacy when compared to their previous experiences with other drugs. These findings are in keeping with other reports.

The effects of perphenazine on specific symptomatology were more encouraging than the general therapeutic results. The most dramatic was the effect on behavioral disturbance (Table III). Here one observed a profound decrease in psychologically determined hyperkinesis. Although no data were obtained related to the general problem of hypokinesis (with the exception of catatonia) it was our impression that there was a tendency of the drug to normalize this motility disorder. Certainly catatonia was profoundly reduced and in five of the nine patients who showed this symptom there was a return to near normal motility. It must be noted, however, that several of the catatonics had residual symptomatology in other areas which to a slight extent influenced their general level of activity. All of the behavioral disturbances were affected in over 50% of the patients with the exception of tremor.

Changes in affect (Table IV) induced by perphenazine were interesting. Decrease in pathologic elevation of feeling tone was observed in 85% of patients with this symptom. Unexpectedly, 42% with depressed affects reported an improvement of mood (feeling tone rather than content). This finding is noteworthy in that this study, which was done prior to the availability of imipramine, demonstrated that a phenothiazine drug may have a marked antidepressant action which was most pronounced in the patients with major affective disorders. This observation is in contrast to the reports of Ayd[3] and Cahn and Lehman[4] who observed no effectiveness in depressions.

Verbal activity (Table V) whether increased or decreased was normalized in approximately 50% of the patients. This change was particularly pronounced in the affective disorders where the increased quantity of speech was reduced in almost all patients who had a change of feeling tone.

Ideational distortions (Table VI) as manifested by delusions were not profoundy affected by perphenazine with the exception of persecutory delusions. These were reduced in over 50% of cases irrespective of diagnostic group. Affectively determined delusions of guilt, unworthiness, and of somatic disturbances were least influenced. Hallucinations (Table VI) responded promptly to medication, particularly in the organic psychoses, and visual hallucinations were reduced in over 50% of the patients with schizophrenia and affective psychoses. Auditory hallucinations on the other hand responded less well in these two diagnostic categories.

Finally sensorial (Table VII) disturbances did not respond to the medication as did other manifestations of the illness. This was particularly true in delirium tremens where the response of visual and auditory hallucinations was often dramatically prompt. The persistence of the sensorial disturbances for a short while longer indicated a need for continued nursing management and care after

TABLE I

Diagnostic Grouping of 196 Patients

NEUROSES:	
Anxiety reaction	27
Depressive reaction	22
Other types	6
Total	55
AFFECTIVE DISORDERS:	
Manic-depressive—depressed	24
Manic-depressive—manic	14
Psychotic depressive reactions	12
Total	50
SCHIZOPHRENIA:	
Simple	3
Hebephrenic	6
Paranoid	29
Catatonic	5
Undifferentiated	13
Szhizo-affective	6
Total	62
BRAIN SYNDROMES:	
Acute	18
Chronic	11
Total	29

TABLE II

General Therapeutic Results

	Number	0%	25%	50%	75%	100%	Worse
NEUROTIC REACTIONS							
Anxiety	27	8	4	6	3	2	4
Depression	21	7	5	3	3	1	2
Other	6	2	3	1	–	–	–
AFFECTIVE DISORDERS*							
Manic-depressive—depressed	21	8	10	–	–	–	3
Manic-depressive—manic	6	1	–	–	4	1	–
Psychotic depression	12	6	–	2	3	1	–
SCHIZOPHRENIA							
Simple	3	2	–	1	–	–	–
Hebephrenic	6	2	1	1	–	1	–
Paranoid	29	9	3	10	3	3	1
Catatonic	5	2	1	1	–	1	–
Undifferentiated	13	3	7	1	–	–	2
Schizo-affective	6	2	–	2	1	1	–
ORGANIC							
Acute	18	–	3	3	2	10	–
Chronic	11	6	–	1	3	1	–
Total	184	58	37	32	23	22	12
% Total		31	20	17	13	12	7
%—50% or greater					42%		

*Based on mood statements.

TABLE III

Behavior

	Agitated	% Change	Combative	% Change	Excited	% Change	Tremulous	% Change	Hyperactive	% Change	Catatonic	% Change	Hostile	% Change	Other	% Change
NEUROTIC REACTIONS																
Anxiety	12	58	–	–	3	66	6	0	5	20	–	–	2	50	1	0
Depressive	11	55	–	–	3	66	2	50	7	29	–	–	4	50	1	0
Other	3	100	–	–	2	50	1	100	2	50	–	–	1	100	1	0
AFFECTIVE DISORDERS																
Manic-depressive—depressed	11	63	2	0	6	33	1	0	6	66	–	–	5	40	4	0
Manic-depressive—manic	11	63	2	100	11	72	2	0	14	71	–	–	7	57	3	33
Psychotic depressive	5	60	1	100	3	66	2	50	4	75	–	–	2	50	2	0
SCHIZOPHRENIA																
Simple	1	0	–	–	–	–	–	–	1	0	–	–	–	–	–	–
Hebephrenic	3	0	1	100	2	50	1	0	1	100	2	100	1	0	1	0
Paranoid	17	65	1	100	4	50	4	50	8	63	1	100	17	65	2	0
Catatonic	2	0	1	0	–	–	1	0	0	0	4	75	1	0	–	–
Undifferentiated	3	0	–	–	3	0	1	100	1	100	2	0	3	33	3	33
Schizo-affective	5	60	1	0	3	100	1	0	3	0	–	–	2	50	2	0
ORGANIC																
Acute	16	87	1	100	8	75	6	100	6	67	–	–	5	100	1	0
Chronic	3	67	2	50	3	66	4	0	4	50	–	–	5	60	–	–
Total No. with symptoms	103		12		51		32		62		9		55		21	
% Change*		61		58		68		38		55		67		58		9

*Represents % of patients with symptoms who improved 2+ or more.

TABLE IV

Mood

	Elated	% Change	Depressed	% Change	Anxious	% Change
NEUROTIC REACTIONS						
Anxiety	2	0	18	33	13	46
Depressive	–	–	21	38	4	0
Other	–	–	5	100	1	100
AFFECTIVE REACTIONS						
Manic-depressive—depressed	–	0	19	47	3	0
Manic-depressive—manic	14	85.7	2	0	2	50
Psychotic depressive	–	–	11	55	4	75
SCHIZOPHRENIC REACTIONS						
Simple	–	–	1	100	–	–
Hebephrenic	–	–	3	33	2	0
Paranoid	4	50	9	11	11	27
Catatonic	–	–	3	0	1	0
Undifferentiated	–	–	5	0	4	50
Schizo-affective	3	67	4	50	2	100
ORGANIC						
Acute	–	–	7	100	9	67
Chronic	–	–	6	33	4	75
Total Number	30		114		60	
% Change		53		42		45

alleviation of the more dramatic hallucinatory manifestations.

The side effects and toxic manifestations of the drug are summarized in Table VIII and confirm previous observations, i.e. perphenazine produces dyskinetic symptomatology in a high percentage of patients. Retrocollis, torticollis, and akithesia occurred frequently in spite of the routine administration of anti-Parkinson drugs. The low incidence of hepatic disturbance is also worthy of note, as all patients were routinely followed for evidence of hepatic dysfunction. No jaundice was observed and changes in liver function tests showed themselves initially in the thymol determinations and were not accompanied by clinical symptoms. With reduction or discontinuance of the drug, these tests returned to normal. The one dermatologic response was a macular rash which disappeared with discontinuance of medication and reappeared when the medication was again prescribed.

TABLE V

Verbal Activity

	Reduced	% Improved	Increased	% Improved
NEUROTIC REACTIONS				
Anxiety	1	0	7	14
Depressive	3	33	4	50
Other	–	—	2	50
AFFECTIVE REACTIONS				
Manic-depressive—depressed	1	0	10	40
Manic-depressive—manic	–	–	14	69
Psychotic depressive	–	–	3	66
SCHIZOPHRENIC REACTIONS				
Simple	1	100	–	–
Hebephrenic	2	100	3	0
Paranoid	2	50	17	53
Catatonic	4	50	–	–
Undifferentiated	1	100	4	25
Schizo-affective	2	0	5	60
ORGANIC				
Acute	–	–	8	62
Chronic	1	0	4	0
Total Number	18		81	
% Change		45		48

Conclusions

Perphenazine resulted in desirable, but not complete symptomatic changes in the above described areas. The best responses for a specific diagnostic group were seen in the acute brain syndromes in which improvement was dramatic and apparently specific. Although ideas of guilt and unworthiness were not relieved in the depressed manic-depressive or psychotic-depressive patient, improvement in feeling tone did occur in

47% of the depressed manic-depressives and 55% of the psychotic-depressives. Dramatic decreases in the level of feeling tone were observed in patients with elation. It is concluded that perphenazine is a useful and effective chemotherapeutic agent in a wide variety of psychiatric disorders and is relatively non-toxic.

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TABLE VI

	DELUSIONS										HALLUCINATIONS					
	Persecution	% Change	Guilt	% Change	Unworthy	% Change	Grandeur	% Change	Somatic	% Change	Visual	% Change	Auditory	% Change	Other	% Change
NEUROTIC REACTIONS																
Anxiety	3	100	3	33	3	33	0	—	3	—	1	—	1	—	1	—
Depressive	4	—	6	66	4	50	—	—	3	100	–	—	1	—	1	—
Other	1	—	1	—	2	—	—	—	2	—	–	—	1	—	1	—
AFFECTIVE DISORDERS																
Manic-depressive—depressed	2	0	7	0	10	10	2	—	7	—	–	—	—	—	–	—
Manic-depressive—manic	3	33	2	50	2	50	2	—	1	—	4	50	3	33	–	—
Psychotic depressive	2	100	3	33	2	50	—	—	3	—	–	—	—	—	–	—
SCHIZOPHRENIA																
Simple	1	50	–	—	1	—	—	—	1	—	–	—	1	—	–	—
Hebephrenic	3	66	1	—	1	—	1	—	–	—	–	—	4	75	1	—
Paranoid	19	66	8	—	4	25	11	54	7	57	7	57	11	36	1	100
Catatonic	2	—	1	100	1	100	—	—	–	—	–	—	2	—	–	—
Undifferentiated	6	66	4	25	1	100	2	—	5	—	–	—	5	80	2	—
Schizo-affective	2	100	6	33	2	50	4	50	3	—	2	—	3	33	2	—
ORGANIC																
Acute	4	75	3	33	1	—	1	—	1	—	9	—	9	77	2	50
Chronic	3	—	1	—	1	—	—	—	4	—	2	100	1	100	–	—
Total Number	56		47		35		24		41		25		42		11	
% Change		52		32		31		33		17		64		50		18

TABLE VII

Sensorium

	Calculation	% Change	Memory	% Change	Orientation	% Change
NEUROTIC REACTIONS						
Anxiety	2	0	2	0	2	0
Depression	1	100	1	100	2	50
Other	1	0	1	0	1	0
AFFECTIVE DISORDERS						
Manic-depressive—depressed	1	0	–	–	–	–
Manic-depressive—manic	1	0	1	0	1	0
Psychotic depression	1	0	1	0	1	0
SCHIZOPHRENIA						
Simple	–	–	–	–	–	–
Hebephrenic	1	0	2	0	2	0
Paranoid	2	0	4	0	1	0
Catatonic	–	–	–	–	–	–
Undifferentiated	2	–	1	–	1	–
Schizo-affective	–	–	–	–	–	–
ORGANIC						
Acute	18	33	18	33	18	35
Chronic	2	0	2	0	4	0
Total Number Patients	32		33		33	
% Change		22		21		24

TABLE VIII

Complications—184 Patients

	No.	%
Hepatic	3	1.6
Hematologic	2	1.0
Blood pressure	6	3.3
Dermatologic	1	0.5
Dyskinetic	66	36.0
None	106	57.6

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Is Ritalin an Addiction-Producing Drug?

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Since its discovery by Meier et al. in 1954,[1] methylphenidate (Ciba-Ritalin) has been the subject of many favorable reports. It has been used in depression both functional or chemically induced,[2-6] as the treatment of choice in narcolepsy,[7] and as a valuable adjuvant in psychotherapy and in psychiatric diagnosis.[8] The indications for Ritalin are derived from analeptic qualities which parallel those of amphetamine, without sympathomimetic repercussions, and from a drug potency lying between amphetamine and caffeine. Average doses range from 10 to 20 mg., two or three times daily,[5,6] and the effects last approximately four hours.[5]

Unlike the more powerful stimulants, Ritalin does not reportedly produce the untoward effect of addiction. Lacking proof, this possibility has only been mentioned without actual reference to the case involved.[2,5] Therefore, on the occasion of a recent case of Ritalin abuse, this possibility should be investigated in the light of the newly proposed criteria for addiction as opposed to simple habituation.

As defined by the World Health Organization, addiction is a state of periodic or chronic intoxication, detrimental to the individual and to society, and which is produced by the repeated consumption of a drug. Its characteristics include: 1. An overpowering desire or need ("compulsion") to continue to take the drug and to obtain it by any means; 2. A tendency to increase the dose; 3. A psychological and sometimes physical dependence on the effects of the drug.[9,10]

By the "tendency" to increase the dose is meant the phenomenon of tolerance whereby more and more of a substance must be used to reproduce its initial effects.[11] "Psychological dependence" refers to the substitution of a drug for other types of adaptative behavior, the addict seeking refuge in his drug rather than looking for a constructive approach to his problems.[12] "Physical dependence" pertains to the altered physiologic state which requires continued administration of a drug to prevent the appearance of an abstinence syndrome; physical dependence, however, does not constitute a necessary feature of the condition of addiction.[12,13]

The above criteria for addiction apply to the depressants of the central nervous system more readily than to stimulants like Ritalin. Actually, the stimulants do not as yet constitute a well defined group of addiction-producing agents. They possess no common chemical denominator and are not related other than in their excitant action on the central nervous system.[14] As a pharmacological action, stimulation lacks the powerful addictive potentiality of the narcotics. It is believed for example, that irrespective of personality factors, the specific pharmacological action of morphine will always produce—under individual conditions of time and dose—"compulsive" craving, dependence

and addiction in the subject.[10] However, addiction to stimulants can apparently occur without tolerance, physical dependence, or abstinence syndrome,[12] although tolerance to amphetamine has been reported to develop rapidly.[15] There is no necessity for withdrawal treatment.

In general, the stimulants are responsible for a form of addiction that is relatively benign,[15] and certainly less serious than the chronic intoxication by the narcotics or even by the barbiturates.[16] This type of addiction occurs infrequently. In a classic study, only seven cases of addiction to amphetamine were reported with seven others found in the literature.[15] Characteristically, increased doses of stimulants tend to produce a toxic psychosis with paranoid delusions.[12] The personalities and dynamics involved in the addiction to stimulants are not as sharply delineated as for addiction to depressants.[17,18]

To emphasize the rather mild addictive qualities of the stimulants, it is often necessary to contrast them with the simple habit-forming drugs, which may be taken repeatedly without producing the characteristics outlined in the definition of addiction. The repeated use of the habit-forming drugs is not considered detrimental to society.[9,10] If they cause any detrimental effect, it is to the individual alone.[19] They have no sedative or stimulative action, e.g. vitamins; or, if they do, it is below the required threshold for addiction. In the habituation to drugs, paramount psychological factors are at work by opposition to adjuvant pharmacological action. Users commonly regard these drugs as a kind of soteria (Laughlin's term for the converse of phobia to denote the security attached by a person to certain objects).[20] Paradoxically, the effects of habit-forming drugs may amount to a syndrome of "addiction without drugs."[21]

Like mild depressants, the stimulants are an intermediate group of drugs, which may initiate addiction or habituation, depending on the interplay between the pharmacological action of the drug and the psychological make-up of the user. In this group, the user's psychological make-up is the determining factor of addiction or habituation, but a significant role is played by the pharmacological action of the drugs.[10] There is enough stimulative potency in the drugs to induce addiction in predisposed individuals. Without this addictive factor there could be no addiction "to drugs." Even if at the minimum degree, it is always present in the drugs of this group.

Amphetamine derivatives illustrate this hybrid group of drugs. They are credited with the capacity of causing addiction.[10,15] Yet, they may also be used in a manner which must be termed habituation. Consider the following cases:

Case 1: A 45-year-old business executive showed a poor adjustment toward his employer and was chronically depressed. Because of this condition, he believed it necessary to have the two yearly vitamin injections he religiously received. Additionally, he has taken one Dexamyl (Dexedrine 5 mg., and Amobarbital 32 mg.) every morning for the last five years. If he forgets his medication, he will hurry back from work to correct his mistake. No untoward effects due to this medication have been seen.[22]

Case 2: A 77-year-old successful lawyer had been accustomed to taking Desbutal (Desoxyne Hydrochloride 5 mg., and Sodium Pentobarbital 30 mg.) for the past 10 years whenever faced with a special task or problem. As he had a busy practice, it is a rare day that he did not take one to three Desbutal. While this man is considered chronically depressed, no untoward effects can be ascribed to his taking Desbutal over the years.[23]

With these considerations in mind, the case of a patient believed to have been addicted to Ritalin is presented.

Case 3: Two weeks following the sudden death of her mother, an unmarried 37-year-old woman stenographer was hospitalized because of excessive use of Ritalin during a year-and-a-half period in which she had taken the drug in order to counterbalance mounting inferiority feelings.

After admission, the patient was concerned only with obtaining Ritalin. With ingenious variations she appealed repeatedly for the medicine. When she visited her physician, she looked to him for the drug, but did not furnish the cooperation which would lead to an evaluation of her problems. She outlined her history, but significant details had to be filled in by her brothers and by her hospitalized sister. She played down the seriousness of her consumption of Ritalin in the face of her own belief that it had killed her mother. This belief was a contradiction of her opinion that Ritalin was "good." For a long time the patient maintained the request that the drug, in substitute if not in form, was the sole treatment for her condition.

As she met with no success, she attempted to divert temporarily the notorious role Ritalin had played in her life and placed the beginning of her illness many years in the past. She stated that from the age of 23 to 31 she had suffered from a "depression" and had been obsessed by the idea of being unaccepted by her co-workers for the very reason that she was unacceptable. Fighting the fear that she might kill someone, she had remained at her job following a psychiatrist's advice to do so. After her sister's hospitalization for schizophrenia, the patient started to believe that everybody on the street was looking at her face. Her forehead was supposed to be "bad and angry-looking" in contrast to the lower part of her face which was "still good." After leaving her steady job, she worked periodically "at some hundred places" until two years ago when she practically discontinued all remunerative occupations.

Eventually, though reluctantly, the mother reportedly permitted the patient to be admitted to a private sanitarium for a stay of one month. At the time of discharge, the recommended medication was two 10 mg. tablets of Ritalin, three times daily.

Notwithstanding three subsequent readmissions, the patient claims great help from the medication because "it increased my self-confidence to the point of feeling human like other people." Soon she requested and was granted the permission to raise the dose each time by one-half tablet. By that permission she believed herself authorized to adjust the dosage to her own requirements and actually to greater and greater proportions in order to maintain the effects of initial doses. Thus, in the months preceding her commitment to the hospital, she was taking up to 125 tablets Ritalin daily.

She would take eight tablets followed by one soneryl (the soneryl being added for the relief of palpitations after she had taken six tablets at one time) and would become stimulated as desired. Feeling less stimulated after an hour or so, the patient would consume eight more Ritalins with one more soneryl practically every hour. At bedtime the patient resorted to four soneryls. The procedure was repeated for five days. The patient reportedly did not continue further because of her incapacity to be aroused anymore. The medication thus forcibly discontinued, she would enter a four or five day depressed period ushered in by a half-hour crying spell that nothing could stop. The depression over, the patient would resume the use of the drug in the same manner.

Meanwhile, the repercussions of the patient's periodic intoxication with Ritalin and of her desire to obtain it by any means were felt by the entire family, especially the mother. The patient requested money from everyone. A check was discovered in the patient's name which the mother, dying from an acute coronary thrombosis, had been unable to complete. The patient's adverse reactions from the Ritalin were no less striking. In her rare attempts to return to work, she found her fingers seemingly paralyzed on the typewriter by the hyper-stimulation from the drug.

The patient's past history throws some light on her need for Ritalin. She had always been a shy and retiring person. Her important human role was played in her family where she became the center of attention in the following manner.

At an early age, her four older brothers had been invested with their father's authority who, in spite of a few emotional protests, let himself be dominated by his wife. Under the pretext that "this was necessary to help the girls," the mother satisfied her selfish aspirations as their supposed one and only true provider of love. Being unable alone to give her daughters all that she conceived a good parent should give, she compelled the rest of the family to implement her protective tendencies and she assumed the sole merit for the results. In final analysis, the rule applied exclusively to the patient since her older sister had to give in to her.

According to these maternal standards what the patient thus received she had to consider her due. She did not have to show any gratitude to her siblings as givers and she never hesitated in blackmailing them into giving more favors. To retain the preferential treatment, she had to pay lip service to her mother's uniquitous solicitude. With enough encouragement and enough guilt suggested, her mother "would have given me the moon." Literally, the patient would have accepted the offer, for she had to be always on the receiving end. In that respect, her familial role is said to be reduplicated in her present expectations from Ritalin. Like her mother, the drug is regarded by her as an inexhaustible source of narcissistic supply.

Discussion

It would seem that the question: Is Ritalin an addiction-producing drug, can, in a way, be answered affirmatively in the above case. Given another person, it might have brought on a simple state of habituation. Nevertheless, the kind of Ritalin abuse demonstrated by this patient pertains to addiction. In her history, such conditions of addiction as defined by the World Health Organization are fulfilled. Even more remarkable, the phenomenon of tolerance, not always so obvious in addicts to stimulants as it is in addicts to depressants, is unequivocally present here. The very possibility of abstinence syndrome, which implies a physical dependence on the drug, cannot be altogether excluded and speaks in favor of the addictive character of the case.

It can be objected that for lack of Ritalin other addiction-producing drugs would have been used by the patient as a defensive measure against her schizophrenic tendencies. In this sense, the choice of Ritalin as an addiction-producing agent was accidental. But not otherwise. Ritalin had enough addictive strength to be chosen by the patient as an addictive agent. After receiving a probable initial help from the pharmacological action of the drug alone, the patient transcended the confines of stimulation as Ritalin became the sole interest of her life, the one center of her activities and human expectations.

Conclusion

Strictly speaking, from the point of view of the drug itself, Ritalin belongs to the group of drugs with the dual potentiality of addiction and habituation. From the point of view of the patient in Case 3, a condition of addiction and not a simple habit was developed while taking Ritalin in excess of the prescribed dosage. The case can be labeled "borderline." But, whatever it may be, drugs like Ritalin are bound to cause addiction in the future. As far as there is addictive power in a drug, addiction cannot be avoided. If possible, the measurement of what constitutes the minimum of addictive ingredient in a drug would be an interesting research venture.

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The Substratum of Memory

I. E. LICHTMANN, M.D.

The indispensable role of memory as the foundation of practically all mental processes is generally recognized and requires no further proof. Memory may also be called the bridge between past and present, and a new arrangement of its parts may contribute to building up the pathway to the future. The word "memory" itself probably belongs to the oldest inventory of language, and yet, its substratum is still unknown. All scientists working in the realm of mind exploration, whether they are philosophers, psychologists or neuro-psychiatrists are in agreement. This relationship was acknowledged in the "Symposium on Brain and Mind,"[1] in Laslett's "The Physical Basis of Mind,"[2] and in Adrian's "Physical Background on Perception."[13]

In spite of our ignorance of the basic principles of memory, its various manifest disorders have some differential diagnostic significance in certain neuropsychiatric disease such as retrograde amnesia or in the differentiation of recent or remote events. Thanks to Penfield[1] and his co-workers, scientists now at least know some facts about the topographical anatomy of memory and may even elicit some fragments of remembrance experimentally.

Before presenting a physical analogy of the action of the receptor organs (sense organs) one fact must be stressed. The receptor organs are indispensable to the foundation and development of memory. If there are no receptor organs, there is no memory. For the present purpose, however, it makes little difference whether we use the old classification of receptor organs or Sherrington's[4] grouping of exteroceptors, interoceptors, and proprioceptors. Of course, once memory is established, the cooperation of the receptor organ itself (eye, ear, etc.) is no longer necessary as far as the mere maintenance of memory is concerned. Any extension of memory requires again the cooperation of the receptor organ involved.

Another fact must also be mentioned. Neural connections between the receptor organ and the corresponding ganglia within the cerebral cortex will conduct electric energy only. The receptor organ not only has to receive the stimuli but also transform them to appropriately modified electric signals to be conducted to the corresponding cerebral ganglia via the related axon cylinder. The frequency of potential changes within the axon cylinders[5] and ganglionic cells, up to a hundred per second, is entirely compatible with the continuously changing patterns of new visual, auditory or any other sensory stimuli.

Before offering an explanation of the events occurring within the cerebral ganglia it will be helpful to review an experiment first performed by Chladni,[6] and since repeated and confirmed by other scientists. Chladni, interested in the visualization of acoustic waves caused sand to be strewn over a metal plate which was clamped at its center. A violin bow was then stroked along the outer edges of the plate and the resultant vibrations of the plate moved the sand particles into various patterns or designs. The simplicity or complexity of the patterns formed by the sand depended on the vibrations of the plate and illustrated the formation of nodes and segments on the vibrating plate. In honor of the discoverer, these patterns are now called "Chladni's" sound figures to describe the events occurring inside the cerebral ganglia. The plate matches the membrane covering the ganglionic body, the sand strewn upon the plate corresponds to the different molecules within the ganglion, and the violin bow the electric current coming from the axon cylinder and flowing into the ganglion. Even the clamped center of the plate has its counterpart in the nucleus of the ganglion.

As memory is the basis of practically all mental processes so the stock for memory

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consists of all the gained and gathered sensory experiences. Thus, to continue the analogy sketched above, identical stimuli arriving at the receptor organ are transformed into identical electric stimuli which finally flow into the ganglionic bodies. These identical electric stimuli will bring about an identical arrangement of the molecules within the ganglionic bodies. The repetition of identical arrangements of the molecules within the corresponding cerebral ganglia forms the "substratum of memory." The present writer presents then the following hypothesis: Identical stimuli will produce identical potentials which in turn will produce identical arrangements of the molecules inside the ganglionic bodies. The formation of identical pattern of intra-ganglionic molecules is the "substratum of memory."

This theory refers, of course, to a "one track" memory such as is present in smell or taste, or to higher developed receptor organs, e.g. sight, in the first stage of its formation. Later on, when speech, reading, and writing develop, they also require memory in more complicated form. New pathways have to be established but the basic principle remains the same. It is then conceivable that the entire process of learning has the identical substratum, i.e. the potentiality of a different arrangement of the molecules inside the corresponding ganglia.

Should this theory be acceptable, the way may then be paved for a better understanding of such neuropsychiatric phenomena as the retrograde amnesia after an epileptic seizure, after cerebro-vascular accidents or trauma, or after EST. Once there is some concrete knowledge of the exact chemical structure of ganglionic bodies many cases of functional mental disease may have a better chance of improvement. Some of these diseases along with host of other neuropsychiatric illnesses could then be placed above one common denominator, an impaired memory.

To array as many facts as possible above a common denominator is indeed one of the most important tasks of science. The present writer thinks, therefore, such a high mental characteristic as memory could be understood from the properties of certain brain cells. Changeable arrangements of molecular settings may then be called the language of the body.

Summary

1) The cooperation of receptor organs is indispensable as a foundation of memory.

2) The receptor organ has two functions —(a) the reception of adequate stimuli and (b) their transformation into electrical potentials to be conducted within the corresponding axon cylinder.

3) In analogy with Chladni's sound figures, the molecules within the corresponding ganglion cells are continuously changing their arrangement corresponding to the potentials arriving from the axon cylinder.

4) Those continuously changing patterns inside the ganglia are the "substratum of memory."

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BOOK REVIEWS

THE PHYSICIAN AND THE LAW: Rowland H. Long. Second edition. New York, N. Y.: Appleton-Century-Crofts, Inc., pp. 302.

The author's introduction to his book advises its objective as being twofold: 1) to afford the physician some knowledge of the rules of law which govern the physician-patient relationship; 2) to help the physician who has to appear in court as a witness.

However in a further paragraph, the author appears to have revised the book's purpose. While he still clings in part to its avowed aim, the author's decision indicates a later conclusion that "lawyers may also find it helpful."

In the foreword which directly follows the introduction, we find that the book is intended for the instruction of medical students (physicians in future) in understanding the important phases of legal medicine; and it is further suggested that the book may be used to enlighten the lawyer about topics in medicine and to furnish consequent legal citations.

No claim is made by the author, who is not a physician, that the book is in any way a treatise in any branch of medicine. Nevertheless he has advised the reader both in the introduction and on page 152 of the book proper, that material therein, which has taken up some 50 pages of space, has been reproduced from a medical work titled *Legal Medicine, Pathology and Toxicology* authored by four physicians who are pathologists. Thumbing through these 50 pages we find such redundant matter—of no need by the practising physician who has to appear in court as a witness—as: Determination of cause of death because of interference with the organs which maintain the oxygen cycle, medullary centers, blood, respiratory and circulatory systems; unexpected and sudden natural deaths; recognition of the cause of death; classification and statistics of sudden and unexpected natural death; (grouped according to pathologic anatomy and etiology); summary of lesions causing sudden and unexpected natural death. 1. Diseases of the Heart and Aorta, (individually listed); 2. Diseases of the Respiratory System (individually listed); 3. Diseases of the Brain and Meninges (individually listed); 4. Disease of the Digestive and Urogenital apparatus (individually listed); 5. Miscellaneous Diseases (individually listed); 6. Children—diseases and anomalies (individually listed). Natural Death and Trauma; Types of Trauma; Influence of Alcohol on Trauma; Blunt Force Injuries; Homicidal, Suicidal and Accidental Deaths; Stab Wounds; Skin Lesions; Necropsy; Velocity and Wounding Power of Bullets; Wound of Entrance; Wounds of Exit; Repair of Bullet Wounds; Necropsy Procedure; Homicidal, Suicidal, and Accidental Bullet Wounds; Hanging as a form of strangulation.

As will be seen from the captioned abstracts, this reading matter, while interesting, may be read by the physician in an appropriate text conforming to the standards of a descriptive work on forensic aspects of pathology and toxicology. However, medical abstracts of this sort have no place here, nor can they usefully enlighten the lawyer.

Moreover, in his Chapter 6, the author's discussion of the subject of autopsy includes wasteful reading matter which will not help the physician who has to appear in court as a witness, inasmuch as it reproduces in toto sections of the New York City Charter as they relate to the Office of the Chief Medical Examiner.

One section delineates: Organization of office, officers and employees, includes the manner an officer or employee may be removed and the periods when the office shall remain open. Another section delineates: Violent and suspicious deaths—procedures. Another section delineates: Autopsies—Findings by the Medical Examiner's office. Another section delineates: Report of deaths, removal of bodies. Another section delineates: Oaths and affidavits administered by Medical Examiner. Surely, the reading of the mechanics of legal function of the Office of Medical Examiner of New York City will be of no use to the practising physician who has to appear in court as a witness; nor can it be used to enlighten an attorney, who, by virtue of his education and legal training is deemed to know the law, or to be able to find the applicable sections which may best serve the matter which he is engaged in litigating.

Chapter II on Baby Adoption, which covers five pages of textual material, is not within the physician's province, except as he or as any other person so minded, may become active in the procurement of babies for adoption through the various black and gray baby markets. This subject, not being a medical problem and therefore of no medical concern to the ethical practitioner, could have well been deleted in a book designed by the author to help the physician who has to appear in court as a witness.

Chapter XV on Insurance, speaks of three kinds of liabilities: 1. malpractice insurance; 2. automobile liability insurance; 3. public liability insurance; as well as other types, not excluding life insurance under various plans of coverage. The Chapter covers some nine pages of text, which is at best a smattering of the subject of insurance, has nothing to do with a medical problem, and as such, again has no necessary place in a book of this kind. If a physician wants to place insurance he had best consult his trustworthy insurance source before learning from the latter what is the most advantageous protection to the physician-purchaser.

Although the author's revised recommendation is that the book is also for lawyers' use, the glossary

therein merely defines a short listing of simple Legal and Insurance terms.

The book, exclusive of the redundant material adverted to, is well written, is in simple language, has liberal case reference material at the end of each chapter, and contains a useful representative index. In this reviewer's opinion the book can be of no assistance to the lawyer, but may be used with benefit by physicians, particularly by those who may have to appear in court as a witness.

Lewis J. Siegal, M.D., LL.B.

PROGRESS IN NEUROLOGY AND PSYCHIATRY, VOL. XIV: Edited by E. A. Spiegel, M.D. New York: Grune & Stratton, 1959. Pp. 656. $12.75.

With the advent of growth of interest in the action and psychopharmacologic effects of the new drugs as psychotropic prototypes acting on the brain and consequent functional aspects, the author has included a review of the most knowledgeable extant data respecting the biochemistry of cerebral neurophysiology. The chapter on neuroophthalmology is new, and is neurologically enlightening in view of the progress which has been made in the neuroophthalmologic diagnostic armamentarium. Attention is called to the indications for electrooculography and the importance of its use is emphasized as an index of retinal function particularly in such affections as microphthalmus, retinitis pigmentosa, cicatricial chorioretinitis and retinal detachment.

The character of neuroorthopedics is new, and while it represents an area where orthopedics, neurosurgery and neurology must of necessity overlap, the chapter nevertheless develops points of view peculiar to the difficult clinical situations in this area. Discussed, are such problems as recent trends respecting the treatment approach in infections of the spine, with criteria dependent upon the degree of neurologic involvement. There is evaluation of the problem of spinal fractures and dislocations which points up the possibility of mistaking anomalies of this structure, which may mimic and sometimes become associated with fracture-dislocations.

The subject of fusion against nonfusion is expertly weighed within this chapter, as well as consideration of conditions which are either actual diseases of bones and joints, or frequently result, or mimic neurologic disorders e.g. compression neuropathies occasioned by a multiplicity of causes requiring intervention by the orthopedic surgeon.

While I have particularly adverted to the newer matter, the book, as a compilation of all-embracing progress, reflects the most salient abstracts of clinical researches and techniques, culled from recent contributions to neurologic and psychiatric world literature.

As in previous years, this 1959 edition continues to present in the most effective form, a current summarization of the literature on the researches and advances in the disciplines of neurology and psychiatry.

Lewis J. Siegal, M.D., LL.B.

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